

AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY

ADVISORY EDITORIAL BOARD

FRED L. ADAIR
BROOKE M. ANSPACH
JAMES R. BLOSS
LUCIUS E. BURCH
WALTER W. CHIPMAN
WILLARD R. COOKE
HARRY S. CROSSEN
THOMAS S. CULLEN
ARTHUR H. CURTIS
WILLIAM C. DANFORTH
WALTER T. DANNREUTHER
CARL H. DAVIS
ROBERT L. DICKINSON

PALMER FINDLEY
C. FREDERIC FLUHMANN
ROBERT T. FRANK
JOHN R. FRASER
WILLIAM P. HEALY
F. C. IRVING
JENNINGS C. LITZENBERG
JAMES C. MASSON
JAMES R. MCCORD
NORMAN F. MILLER
CHARLES C. NORRIS
EMIL NOVAK
EVERETT D. PLASS

ISIDOR C. RUBIN
JOHN A. SAMPSON
OTTO H. SCHWARZ
H. J. STANDER
PAUL TITUS
HERBERT F. TRAUT
NORRIS W. VAUX
GEORGE GRAY WARD
RAYMOND E. WATKINS
BENJAMIN P. WATSON
PHILIP F. WILLIAMS
KARL M. WILSON

OFFICIAL ORGAN

THE AMERICAN GYNECOLOGICAL SOCIETY; THE AMERICAN ASSOCIATION OF OBSTETRICIANS, GYNECOLOGISTS, AND ABDOMINAL SURGEONS; NEW YORK OBSTETRICAL SOCIETY; OBSTETRICAL SOCIETY OF PHILADELPHIA; BROOKLYN GYNECOLOGICAL SOCIETY; ST. LOUIS GYNECOLOGICAL SOCIETY; NEW ORLEANS GYNECOLOGICAL AND OBSTETRICAL SOCIETY; BALTIMORE OBSTETRICAL AND GYNECOLOGICAL SOCIETY; CHICAGO GYNECOLOGICAL SOCIETY; CINCINNATI OBSTETRIC SOCIETY; CENTRAL ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS; AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY; WASHINGTON GYNECOLOGICAL SOCIETY; PITTSBURGH OBSTETRICAL AND GYNECOLOGICAL SOCIETY; OBSTETRICAL SOCIETY OF BOSTON; LOUISVILLE OBSTETRICAL AND GYNECOLOGICAL SOCIETY; SOUTH ATLANTIC ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS; SEATTLE GYNECOLOGICAL SOCIETY; SOCIETY OF OBSTETRICIANS AND GYNECOLOGISTS OF CANADA

EDITOR

GEORGE W. KOSMAK

ASSOCIATE EDITORS

HOWARD C. TAYLOR, JR. . . . WILLIAM J. DIECKMANN

VOLUME 50

JULY—DECEMBER, 1945

ST. LOUIS

THE C. V. MOSBY COMPANY
1945

Copyright, 1945, by The C. V. Mosby Company
(All rights reserved)

*Printed in the United States
of America*

*Press of
The C. V. Mosby Company
St. Louis*

American Journal of Obstetrics and Gynecology

VOL. 50

JULY, 1945

No. 1

Original Communications

CARCINOMA OF THE UTERINE CERVIX*

Interval Report on Treatment, Results, and Complications

GEORGE VAN S. SMITH, M.D., AND RICHARD DRESSER, M.D., BROOKLINE, MASS.
(From the Free Hospital for Women)

THE last paper on carcinoma of the uterine cervix from this hospital covered 780 consecutive, previously untreated, pathologically confirmable cases from Oct. 1, 1902, through 1933.¹ Only those with clearly invasive cancer were included. Our patients with "carcinoma in situ" are treated and followed as a separate group. The present report will summarize the above series, to which have been added three cases as a result of re-evaluating their pathologic sections, bringing the results up to date, and will include a new five-year series of 328 similar cases from Jan. 1, 1934, through Dec. 31, 1938, thus encompassing a total of 1,111 cases. The pathologic sections of this new series have also been carefully rechecked. Acknowledgment is made to the other members of the staff of the Free Hospital for Women for the inclusion of their cases and help in gathering data. Actually, this is a report from the staff. Therapeutic x-radiation was given by Dr. John W. Meachen until the fall of 1937 and since then by one of us (R. D.). For the use of the supervoltage (1,000 kv.) apparatus, we are grateful to the administrators of the Collis P. Huntington Memorial Hospital, now a unit of the Massachusetts General Hospital.

Review of Cases

To facilitate presentation and the comparison and evaluation of results, the whole series is divided into groups according to convenient intervals of time and in relation to changes in treatment. "Hysterectomy" in the tables covers the complete and Wertheim procedures and abdominal excisions of the cervical stump. The postoperative deaths listed in the tables were due to shock, peritonitis, pneumonia or embolism following surgery, and, most often, to sepsis after radium. Embolism and agranulocytosis each accounted for a death after application of radium.

*Presented before the Obstetrical Society of Boston, Nov. 21, 1944.

1902 to 1913 (Table I)

One of the patients, alive at 5 years after treatment, died of cancer of the stomach (clinical diagnosis) 15 months later. Her cervical cancer had been an early one. Another died of diabetes. The 6 patients alive at 10 years were alive at 20 years; 2 were dead of cardiovascular disease at 25 years; the remaining 4, 5 per cent of the whole group, were alive at 29 to 32 years. One of the latter had had metastatic cancer at the bifurcation of the left common iliac vessels and had been operated upon by the late Dr. William P. Graves. There was one complication in this group, a vesicovaginal fistula from radium given for a recurrence. Our purpose in following the survivors longer than really necessary is to obtain information concerning longevity in cured patients and the incidence of new primary malignancies.

TABLE I. SUMMARY OF TREATMENT AND RESULTS, CONSECUTIVE CASES, OCT. 1, 1902, TO 1913, INCLUSIVE

TREATMENT	NUMBER OF CASES	OPERATIVE DEATHS	UNTRACEABLE AT 5 YEARS	ALIVE AT 5 YEARS	DIED OF RECURRENCE BEFORE 10 YEARS	DIED OF INTER-CURRENT DISEASE BEFORE 10 YEARS	ALIVE AT 10 YEARS
Untreated	8		2	0			
Cauterization	37	3	4	0			
Amputation of cervix	6	0	1	2	0	1	1
Hysterectomy	32	5 (16%)	1	8 (25%)	2	1	5 (16%)
Totals	83	8 (11%)	8 (10%)	10 (12%)	2	2	6 (7%)

TABLE II. SUMMARY OF TREATMENT AND RESULTS, CONSECUTIVE CASES, 1914 TO 1918, INCLUSIVE

TREATMENT	NUMBER OF CASES	OPERATIVE DEATHS	UNTRACEABLE AT 5 YEARS	ALIVE AT 5 YEARS	DIED OF RECURRENCE BEFORE 10 YEARS	DIED OF INTER-CURRENT DISEASE BEFORE 10 YEARS	UNTRACEABLE AT 10 YEARS	ALIVE AT 10 YEARS
Untreated	9		2	0				
Hysterectomy	26	3 (12%)	0	11	3	0	1	7
Hysterectomy; radium	11	0	0	2	0	0	0	2
Radium; hysterectomy	10	1 (10%)	1	2	1	1	0	0
Radium	23	0	0	0				
Totals	79	4 (6%)	3 (4%)	15 (19%)	4	1	1	9 (11%)

1914 to 1918 (Table II)

Radium was first used in this hospital late in 1916. The technique of application and dosage employed during earlier years, having been described¹ and now obsolete, will not be given here. Pneumonia caused the death of one patient who was well at the fifth year after treatment. Of the 9 patients alive 10 years after therapy, one died of recurrence 5 months later and one died of presumed recurrence at 14 years and 6 months. Seven, 9 per cent of the group, were alive at 15 years; 2 were dead of cardiovascular disease at 20 years; 2 more were dead of cardiovascular disease at 25 years; the remaining 3, 4 per cent, were well at 27 to 29 years. Complications from treatment occurred in 5 patients: one incisional hernia, one vesicovaginal fistula of surgical origin and one from radium, 2 patients developed both vesicovaginal and rectovaginal fistulas from radium.

1919 to 1923 (Table III)

Of the 14 patients alive at 10 years after therapy, one died 2 months later of recurrence and 3 died of cardiovascular disease before the fifteenth year, leaving 10, 8 per cent, fifteen-year survivors. One became untraceable and one died of sepsis at 18 years and one died of cancer of the stomach (clinical diagnosis) at 19 years and 7 months, leaving 7, 6 per cent, alive at 20 years. Complications: One incisional hernia; two deaths from intestinal obstruction, 13 months and 6 years, respectively, after surgery; and one rectal obstruction from radium given for biopsied recurrence—colostomy was performed, the patient died of cardiovascular disease in her ninth post-radium year.

TABLE III. SUMMARY OF TREATMENT AND RESULTS, CONSECUTIVE CASES, 1919 TO 1923, INCLUSIVE

TREATMENT	NUM- BER OF CASES	OPERA- TIVE DEATHS	UNTRACE- ABLE AT 5 YEARS	ALIVE AT 5 YEARS	DIED OF RECUR- RENCE BEFORE 10 YEARS	UNTRACE- ABLE AT 10 YEARS	ALIVE AT 10 YEARS
Untreated	5		1	0			
Hysterectomy	18	1 (6%)	0	9	5	1	3
Hysterectomy; radium	13	0	0	5	2	0	2
Radium; hysterectomy	2	0	0	0			
Radium	81	1	1	13 (16%)	3	0	9 (11%)
Totals	119	2 (2%)	2 (2%)	27 (23%)	10	1	14 (12%)

TABLE IV. SUMMARY OF TREATMENT AND RESULTS, CONSECUTIVE CASES, 1924 TO 1928, INCLUSIVE

TREATMENT	NUM- BER OF CASES	OPERA- TIVE DEATHS	DIED OF INTER- CURRENT DISEASE BEFORE 5 YEARS	UNTRACE- ABLE AT 5 YEARS	ALIVE AT 5 YEARS	DIED OF RECUR- RENCE BEFORE 10 YEARS	DIED OF INTER- CURRENT DISEASE BEFORE 10 YEARS	UNTRACE- ABLE AT 10 YEARS	ALIVE AT 10 YEARS
Untreated	7			0	0				
Amputation of cervix; radium	1	0	1	0	0				
Hysterectomy	24	1 (4%)	1	0	15	1	2	1	11
Hysterectomy; radium	8	0	0	0	2				2
Radium	186	2 (1%)	6	5	47 (25%)	8	3	1	35 (15%)
Totals	226	3 (1%)	8 (4%)	5 (2%)	64 (28%)	9	5 (2%)	2	48 (21%)

1924 to 1928 (Table IV)

The improved results for this period are attributed to the giving of single doses of 200 or 225 mg. of radium, screened with 0.5 mm. of silver and 0.5 or 1.0 mm. of brass, for 24 to 30 hours, 6,000 mg. hr. being the maximum dose, the brass screening being supplied by the tubes and "pillboxes" used in applying the silver capsules containing the 25.0 or 50.0 mg. of radium.

One patient in this group had primary *carcinoma of the breast* at the time her cervical cancer was treated. The 8 deaths from intercurrent disease before the fifth year after treatment were due to cardiovascular conditions. The 5 deaths from intercurrent disease between the fifth and tenth years were due to the following: cardiovascular disease, 2; pneumonia, 1; peritonitis following operation for primary *carcinoma of the sigmoid*, 1; and primary *carcinoma of the rectum*, 1, this last cancer developing in an area that had been exposed to radium.

Of the 48 patients alive at 10 years, one died of recurrence 15 months later; 5, who were well at 12 to 13 years, became untraceable; and 7 died of intercurrent disease as follows: cardiovascular, 4; pyelonephritis from renal calculi, 1; primary *carcinoma of the vulva*, 1; and *melanoma* of choroid of eye, 1. Thirty-five patients, 15 per cent, were known to be alive at 15 years.

Two patients had complications from surgery, an incisional hernia and a vesicovaginal fistula; and 6 from radium, an obstruction of the rectosigmoid (colostomy, later restoration of intestinal continuity, well at 16 years after radium), a proctitis resulting in stricture, a rectovaginal fistula, a cystitis, a vesicovaginal fistula and a stricture of the ureter resulting in left nephrectomy at 15 years and 2 months.

Fifty-nine, 26 per cent, of the 226 patients in this group had cancers classified as limited to the cervix. Thirty-eight, 64 per cent of them, were alive at the fifth year and comprised 59 per cent of the 64 five-year survivors. The 26, 44 per cent, alive at 10 years comprised 54 per cent of the 48 ten-year survivors. Similarly, the 20, 34 per cent, alive at 15 years comprised 57 per cent of the 35 fifteen-year survivors. Thus, less than 60 per cent of the good results during this period were achieved in patients with a good prognosis based on clinical examination.

1929 to 1933 (Table V)

During this period three changes in treatment were introduced. The first was initiated in the fall of 1930 and consisted of administering radium in 2 doses of 2,000 to 3,600 mg. hr. each, within 10 to 21 days of each other, for a total of 4,800 to 6,000 mg. hr. Early in 1931 the second change was made. Radium applicators of 1.0 mm. brass with additional screening of 1.0 mm. lead were much more frequently employed. Then, in the spring of 1931, x-ray therapy was begun by Dr. John W. Meachen, who used a standard 200-kv. apparatus of that time. His usual procedure was to give four treatments totaling 1,600 r. immediately after the first application of radium and to repeat this in about two months. A third series was quite often administered six to twelve months later and during this interval even a fourth series was sometimes added. Actually, during the years 1931 to 1933, there was a considerable amount of exploratory variation in x-ray therapy as previously described.¹ A gratifying improvement in results ensued in spite of a distressing number of deaths and complications attributable to treatment and an increase of deaths from intercurrent disease.

Three of the deaths from intercurrent disease before the fifth year were from pneumonia, four were of cardiovascular origin, and one resulted from mastoiditis. Between the fifth and tenth years after treatment, 13 patients died of cardiovascular disease and one of suicide.

Deaths From Irradiation.—In the last paper¹ three deaths in this group were attributed to irradiation. Seven deaths are now ascribed to irradiation; four before the third year after treatment, two between the fifth and tenth years, and one at 13 years and 10 months. Irradiation, we feel sure, caused or hastened other deaths but we have not blamed treatment unless the evidence was convincing. Four of the patients dying as a result of irradiation complications had had cancers apparently limited to the cervix. (1) Mrs. M. D. (22,778) died of chronic pelvic sepsis associated with fecal drainage from the cervix one year after the start of treatment. (2) Mrs. J. McK. (21,324) died thirteen months later from the results of ureteral and bowel injury which followed overtreatment, viz., 8,300 mg. hr. and 7,440 r. given over a period of six months. (3) Mrs. E. C. (22,075) died twenty months after first treatment of pyelonephritis from ureteral injury consequent upon retreatment, irradiation reaction having been mistaken for recurrence. No cancer was found at autopsy. (4) Mrs. E. O. G. (23,085) died 2 years and 7 months after first therapy, of hemorrhage into the bladder from the right internal iliac vein, having developed a rectovesical fistula and a sloughing right ureter following an operative attempt to release an irradiation stricture of that ureter. No cancer was found at autopsy. (5) Mrs. R. M. (20,453) had retreatment for presumed recurrence one year after first treatment and a vesicovaginal fistula formed. She died 4 years and 2 months later of pyelonephritis, bilateral ureterostomy for strictures having been performed too late. No cancer was found at autopsy. (6) Mrs. S. W. (22,230) died 8 years and 2 months after primary treatment, of acute ulcerative cystitis, ureteritis, and pyelonephritis. No cancer was found at autopsy. She, too, had received further therapy ten months after first treatment because of suspected persistence of cancer. (7) Mrs. M. G. (19,940) died of pyelonephritis 13 years and 10 months after the start of treatment. Again irradiation reaction had been mistaken for cancer and she had been retreated. She lived fairly comfortably with essential hypertension and a rectovaginal fistula until her thirteenth posttreatment year when, within three months of an intravenous pyelography, one kidney ceased functioning. A vesicovaginal fistula formed. It was too late when cutaneous drainage of the other kidney was perceived necessary. No cancer was found at autopsy.

Complications From Irradiation.—Of those patients dying before the fifth year from treatment, proctitis occurred in 9, a rectovaginal fistula in 1, a rectovesical fistula in 1, and double fistulas in 1. Twenty-six of the five-year survivors suffered a total of 47 complications as follows: incisional hernia, 1; proctitis, 8; rectal stricture, 5; rectovaginal fistula, 5; double fistulas, 2; rectal obstruction, 2; ileitis, 1; cystitis, 18; unilateral ureteral stricture, 3; bilateral ureteral stricture, 1; and vesicovaginal fistula, 1. This simple listing does not give any information about the combination and sequence of complications, so the more serious cases are briefly summarized.

1. *Hysterectomy, radium, and x-radiation:* cystitis at 15 months, stricture of right ureter at 20 months, incisional hernia at 4 years, functionless kidney at 10 years.

2. *Radium:* double fistulas 15 months later following operation for strangulated femoral hernia, cardiovascular death at 6 years.

TABLE V. SUMMARY OF TREATMENT AND RESULTS, CONSECUTIVE CASES, 1929 TO 1933, INCLUSIVE

TREATMENT	NUMBER OF CASES	OPERATIVE DEATHS	DIED FROM RADIATION BEFORE 5 YEARS	DIED OF INTERCURRENT DISEASE BEFORE 5 YEARS	UNTRACEABLE AT 5 YEARS	ALIVE AT 5 YEARS	DIED OF RECURRENCE BEFORE 10 YEARS	DIED OF INTERCURRENT DISEASE BEFORE 10 YEARS	UNTRACEABLE AT 10 YEARS	DIED FROM RADIATION BEFORE 10 YEARS	ALIVE AT 10 YEARS
Untreated	5				0	0					
Amputation of cervix	1	0		0	0	1	0	0	0	0	1
Amputation of cervix and radiation	2	0	0	0	0	2	0	0	0	0	2
Hysterectomy	1	1		0	0	0					0
Hysterectomy; radiation	4	0	0	0	0	4	0	1	0	0	3
Radiation; hysterectomy	1	0	0	0	0	1	1		0		0
Radium	109	4	0	3	4	32 (29%)	2	8	0	0	22 (20%)
Radium; 200-kv. x-radiation	153	0	4	5	0	66 (43%)	4	5	2	2	53 (35%)
Totals	276	5 (2%)	4 (2%)	8 (3%)	4	106 (38%)	7	14 (5%)	2	2	81 (29%)

*Technique of Dr. John W. Meachen (see text covering Table V).

Radium and x-radiation:

- Proctitis at 6 months, stricture at 2 years, rectovaginal fistula at 9 years.
- Proctitis at 7 months, rectovaginal fistula at 11 months, cystitis at 14 months, vesico-vaginal fistula at 17 months.
- Proctitis at 10 months, colostomy for obstruction at 12 months, cystitis at 23 months.
- Proctitis at 10 months, stricture at 5 years, rectovaginal fistula at 9 years.
- Ileitis found on abdominal exploration at 5 years, cystitis at 6 years, recurrent ileitis at 12 years.
- Cystitis at 3 years, severe hematuria at 6 years treated by cystotomy and diathermy excision of diseased area.
- Cystitis at one year, still present at 6 years; left hydronephrosis and functionless right kidney at 6 years and 8 months; left nephrostomy at 8 years.
- Cystitis at 5 years, functionless kidney at 8 years. Except as stated, the above patients were alive 10 to 14 years from primary therapy.

Survival of Patients With Apparently Favorable Cancers.—According to the clinical findings, 88 patients, 32 per cent of the 276 in this group, had tumors confined to the cervix. Sixty, 68 per cent, of them comprised 57 per cent of the five-year survivors, and 50, 57 per cent, of them comprised 62 per cent of the ten-year survivors.

Late Recurrence.—One patient in this group died of proved recurrence at 13 years and 3 months, and another was alive with biopsied recurrence 13 years and 10 months after radiation. Previously¹ we had no proof of recurrence after the twelfth year. It appears that survival for 15 years may be the criterion of absolute cure for this type of cancer.

1934 to 1938 (Table VI)

During this interval there was no change in radium treatment. Two well-screened doses of 2,000 to 3,000 mg. hr. were most often employed. The total dose of x-radiation as given by Dr. Meachen did not exceed 4,800 r. and much more often was 3,200 r. or less because of a fear of complications. Since October, 1937, one of us (R. D.) has administered the x-radiation. The technique of 200-kv. therapy has been as follows: standard apparatus, 50 cm. distance, filter of 0.5 mm. copper, an average of 5 treatments through each of 3 portals,

one 15 × 15 cm. anterior and two 10 × 15 cm. posterior-oblique, for an average total dose of 6,000 r., measured with scattering, given within a period of three weeks. The technique of 1,000-kv. therapy was: 1,000 kv. constant potential, 70 cm. distance, filter of 3.0 mm. lead and 8.0 mm. copper, 15 to 18 treatments in about 3 weeks, delivered through three 10 × 10 cm. portals, one anterior and two posterior-oblique for an average total dose of 7,500 r. measured with scattering. About one-third of the patients in this series received x-radiation before radium.

Deaths From Intercurrent Disease.—The causes of the 22 deaths were: cardiovascular disease, 13 (2 had diabetes); pneumonia, 3 (one of these followed laminectomy for *perincural fibroma* of the spinal cord; no cervical cancer was found at autopsy); peritonitis, 2 (from perforated duodenal ulcer, and following operation for primary *carcinoma of the transverse colon*; no cervical cancer was found at autopsy); chronic ulcerative colitis, 1 (no cancer was found at autopsy); pulmonary embolus following chronic deep phlebitis of the leg, 1; meningitis from neglected middle-ear infection, 1; and suicide, 1. The cancers of 13 of these patients had been classified as confined to the cervix.

Deaths From Irradiation.—(1) Mrs. M. M. (28,816) died of pulmonary embolism 31 days after resection of the rectosigmoid for necrosis developing 5 months after radium. (2) Mrs. M. T. V. (24,607) died of uremia from acute necrosis of the ureters 13 months after combined radium and x-rays. Her cancer had been early. (3) Mrs. G. C. (25,694) died of pyelonephritis associated with severe irradiation cystitis 3 years and 6 months after combined treatment. (4) Mrs. I. M. O. (24,943) died of shock following resection for irradiation ileitis 4 years and 2 months after combined therapy.

Complications From Irradiation.—Minor cystitis and proctitis occurred in 6 patients who died within 5 years of first treatment. Thus far, 36 complications have developed in 27 patients who were alive at 5 years: cystitis, 15; proctitis, 9; ileitis, 3; unilateral ureteral stricture, 3; bilateral ureteral stricture, 1; vesicovaginal fistula, 2; ureterovaginal fistula, 2; and double fistulas, 1. The combination of irradiation followed by radical hysterectomy proved too stringent. Two of the patients so treated got vesicovaginal fistulas. One of them was cured by colpocleisis. A right ureterovaginal fistula and a stricture of the left ureter ensued in another who lost her left kidney and now has a ureterostomy. Right ureterovaginal fistula in another was treated by ureterosigmoidostomy. Of those treated with radium and x-rays before November, 1937, two came to cystotomy and excision of necrotic bleeding tissue. The bilateral ureteral strictures of one patient relaxed without interference. Colostomy and later colpocleisis were a satisfactory solution for the patient with double fistulas. The stenosed ureter in another was effectively dilated from above at the time a temporary nephrostomy was made. Operation was successful in the three cases of ileitis, resection having been performed twice and lateral anastomosis around a localized lesion once. Radiation with 200-kv. x-rays from the fall of 1937 through 1938 has resulted thus far in one case of severe hematuria which cleared with repeated transfusions of whole blood. One patient treated with 1,000-kv. x-rays lost one kidney from pyelonephritis due to stricture of a ureter. She had, however, been overtreated with radium, receiving 7,500 mg. hr.

Incidence of Favorable Cancers.—One hundred and thirty patients, 40 per cent of this series, had tumors that seemed to be limited to the cervix. Ninety-five, 73 per cent of them, comprised 67 per cent of the 142 five-year survivors. Thus, between 1934 and 1938 there was a larger percentage of patients with a good prognosis and proportionately more of them were alive at five years. The disturbing revelation is that there was a smaller percentage of five-year survivors among those with more advanced cancers. It appears that the decreased incidence of complications in this series resulting from a reduction in the amount of x-radiation was accompanied by a failure to save more patients with a poor prognosis.

Cases With Other Tumors.—At the time of cervical treatment one patient in this group had a primary *carcinoma of the breast* and another had wide-spread peritoneal involvement with *papillary adenocarcinoma of unknown origin* (her cervical growth was epidermoid). Two other cases of double primary tumors are included above among those dying from intercurrent disease. One of the five-year survivors had a *papilloma of the bladder* removed by fulguration two years after treatment of her cervical cancer and a primary *carcinoma of the bladder* removed at 4 years and 6 months. (We have now encountered three primary cancers of the urinary bladder in patients previously irradiated for cancer of the cervix or endometrium.) A primary *carcinoma of the ovary* was removed from another patient five years after radiation for cancer of the cervix.

TABLE VI. SUMMARY OF TREATMENT AND RESULTS, CONSECUTIVE CASES, 1934 TO 1938, INCLUSIVE

TREATMENT	NUMBER OF CASES	OPERATIVE DEATHS	DIED OF INTER-CURRENT DISEASE BEFORE 5 YEARS	DIED FROM RADIATION BEFORE 5 YEARS	UNTRACEABLE AT 5 YEARS	ALIVE AT 5 YEARS
Untreated	12		0		0	0
Amputation of cervix	1	0	0	0	0	1
Amputation of cervix; radium; x-radiation*	1	0	0	0	0	1
Hysterectomy	5	0	1		0	4
Hysterectomy; radium	3	0	1	0	0	2
Hysterectomy; x-radiation*	3	0	0	0	1	2
Radium; x-radiation*; hysterectomy	16	1	0	0	0	8
Radium	32	1	1	1	0	17 (53%)
Radium; 200-kv. x-radiation*	191	0	15	3	0	76 (40%)
Radium; 200-kv. x-radiation†	41	0	1	0	1	19 (46%)
Radium; 1,000-kv. x-radiation‡	23	0	3	0	0	12 (52%)
Totals	328	2 (0.6%)	22 (7%)	4 (1%)	2	142 (43%)

*Technique of Dr. John W. Meachen. Cases treated to November, 1937.

†Technique of Dr. Richard Dresser (see text covering Table VI).

‡Technique of Dr. Richard Dresser (see text covering Table VI).

TABLE VII. COMBINED RESULTS

PERIOD	NUMBER OF CASES	ALIVE AT 5 YEARS	ALIVE AT 10 YEARS	ALIVE AT 15 YEARS	ALIVE AT 20 YEARS	ALIVE AT 25 YEARS	ALIVE AT 30 YEARS
1902-13	83	10, 12%	6, 7%	6, 7%	6, 7%	4, 5%	4, 5%
1914-18	79	15, 19%	9, 11%	7, 9%	5, 6%	3, 4%	
1919-23	119	27, 23%	14, 12%	10, 8%	7, 6%		
1924-28	226	64, 28%	48, 21%	35, 15%			
1929-33	276	106, 38%	81, 29%				
1934-38	328	142, 43%					
Totals	1,111	364, 33%	158, 20%	58, 11%	18, 6%		

Total Salvage (Table VII)

As is apparent from Tables I to VI, no statistical corrections have been calculated. The figures for results are as low as can be made and their improvement over the years reflects better treatment despite the errors of commission and omission which will be discussed below. The results with radium and 200-kv. x-radiation in patients treated from January, 1934, to November, 1937 (Table VI), were not so good as those in the 1929 to 1933 group. This is attributed to the reduction in the amount of x-rays because of the fear of complications and a consequent failure to save some patients with more advanced cancers.

Carcinomas of the Cervical Stump

Fifty-eight patients, 5.2 per cent of the whole series of 1,111, had had a supravaginal hysterectomy performed prior to the diagnosis of cervical cancer. Furthermore, 15 patients had had previous bilateral oophorectomy and 8 had had bilateral salpingo-oophorectomy. Five more had had bilateral salpingectomy and two had had both tubes ligated. Thus, 30 patients, 2.7 per cent of the series, developed cancer in the cervix of a uterus that had been rendered a

completely useless organ or one capable only of menstrual function. The implication of these figures is clear.

Discussion

Deaths and Complications From Irradiation.—As might be expected, thin patients have more often had complications than stout. A review of the damage done by therapy (*v.s.*) reveals the following errors:

1. *Overtreatment.*—We now consider anything over 5,400 mg. hr. given in one application and anything over 6,000 mg. hr. given in two applications an overdose of radium. As we use radium, that is, with essentially all beta radiation screened back, we have learned not to leave any amount of it in for over thirty hours unless the indications of the situation outweigh the practical certainty of complications. Despite these restrictions, excessive damage will ensue in some patients even if x-rays are not administered. The maximum relatively safe amount of 200-kv. x-radiation, when combined with the above dose of radium, is 6,000 r., measured with scattering, about one-third of which is delivered to the center of the pelvis. According to our experience thus far, it appears that the maximum relatively safe dose of 1,000-kv. x-radiation is about 7,200 r., measured with scattering, about one-half of which is delivered to the center of the pelvis. The maximum relatively safe daily dose of x-radiation is 400 r. We feel, but have not proved, that it is better to give all radiation within six weeks and to administer x-ray therapy first except in cases with hemorrhage, which is more quickly controlled by radium. If the above amounts of radium and x-rays do not destroy a given cancer, it is likely that more will be ineffective. Of course we are constantly made aware that some patients can tolerate more irradiation than others and that some cancers respond better than others to the same dosage.

2. *Retreatment.*—Mistaking irradiation reactions, viz., edema of the broad ligaments, shaggy rectal ulceration, and perirectal, rectovaginal, and vesicovaginal thickening for persistent cancer, and giving further treatment has been a serious error of the past, although it is impossible to be certain that some retreatments may not have destroyed residual cancer. In general, retreatment is only occasionally really beneficial and, at that, usually only for local vaginal recurrences. Hence it is safer to withhold additional therapy unless the evidence for recurrence is convincing.

3. *Pelvic Surgery by the Abdominal Route After Heavy Irradiation.*—One death in the 1929 to 1933 group followed an attempt to release a stenosed ureter. Another patient in this group developed a ureteral stricture and later lost the function of its kidney from the combination of radiation and hysterectomy. One of the deaths in the 1934 to 1938 group was due to severe local sepsis followed by embolism, resection of the rectosigmoid having been performed after radium. It would have been safer to perform a colostomy. In 1936 one of us (G. V. S.) tried the combination of preoperative irradiation with half the usual amounts of radium and x-rays and then radical hysterectomy. The above-described complications made it seem wiser to give up the experiment.

4. *Delaying Operative Interference in the Hope That Complications Would Improve Spontaneously.*—In retrospect it seems that nearly all the deaths we have attributed to radiation could have been prevented by timely colostomy and/or diversion of the ureters. Since most of the deaths and potentially lethal complications were due to ureteral damage, the development of irradiation

reactions is a signal for repeated intravenous pyelography and preparedness for surgery as long as the patient lives. We now know that ureteral stenosis can occur quickly and at any time up to fifteen years after treatment.

Treatment of Irradiation Complications.—While patients are being irradiated we have in recent years made it a point to increase their vitamin intake, especially of thiamine chloride, but cannot state that they have had less radiation sickness therefrom because the amount of such disturbance varies so much anyway in different patients. Acute postradiation pelvic inflammations have been the cause of nearly all our immediate and early deaths. Fortunately, these have been fairly rare, but we have not yet treated them successfully. Because perforation of the lower bowel is very likely involved, we think pelvic drainage and colostomy may be salutary, along with the modern antibacterial drugs. *Irradiation proctitis:* The tenesmus and pain, though usually of less than two months' duration, are difficult to relieve. One-grain opium suppositories inserted high in the rectum seem to be as effective as anything, along with the maintenance of soft stools. For the usual, not alarming bleeding, iron, liver and high-vitamin diet are prescribed. For the rare profuse and prolonged rectal bleeding, we have found repeated transfusions of whole blood best. The later strictures are gently dilated if they are causing partial obstruction in spite of careful catharsis and the patients are taught to maintain dilatation with a test tube.

Irradiation cystitis: We know of nothing that will hasten its regression or prevent recurrence, but at present are trying frequent instillations of purified cod-liver oil. The patients are given general and symptomatic treatment and watched both for ascending infections and ureteral blockage. Severe and recurrent hematuria is more easily controlled by bed rest and whole blood transfusions than by operative procedures.

Vesicovaginal fistula from irradiation: In a very small experience, colpocleisis has been more successful than direct closure.

Rectovaginal fistula from irradiation: Attempts at closure have failed. Although those who have had colostomy realize how much more satisfactory it is, most patients refuse the operation.

Double fistulas: Providing the ureters are functioning normally and the anal sphincter is competent, our experience with one case indicates that colostomy and later colpocleisis are good procedures. Left transverse loop colostomy is easier to perform than those lower down and just as satisfactory.

Ureteral stricture: Beginning hydro-ureter and hydronephrosis pose a difficult problem. Should immediate attempts at dilatation be undertaken? Irradiation cystitis may make it impossible to find the ureteral orifices. The trauma of cystoscopic dilatation may cause complete blockage, yet dilatation has been apparently successful in a few instances. On the other hand, spontaneous cure has been observed, even when bilateral stenosis was present. If one ureter is functioning normally and the other is becoming progressively stenosed, would it not be better to sacrifice the kidney than to risk the dangers of implanting a pathologic ureter into the bowel or to give the patient the burden of a cutaneous ureterostomy or nephrostomy? Furthermore, implantation into the intestine may be interdicted by proctitis or a rectovaginal fistula. Repeated study and weighing the above considerations in relation to age, general condition, and cancer prognosis will point to the best management. Evidence of renal infection or a rise in blood nonprotein nitrogen mean that the period of expectancy must be terminated.

Status of Treatment.—Bonney,² who has reported on the largest number of radical operations in recent years (500, of a total series of about 800 cases), had 70 operative deaths. This figure, which does not include deaths from complications or their treatment, is considerably larger than that for all the deaths in the above series (surgery, 16 postoperative deaths and 2 later deaths from intestinal obstruction; radiation, 8 early and 11 later deaths) plus the 19 patients with potentially lethal complications who were alive 5 to 15 years after primary therapy. Though we believe, but have not been able to ascertain, that radiation caused or hastened more deaths than we have listed above from that cause, we are sure they would not make the above total mortality even approximate his. In his 300 most favorable cases he had 30 operative deaths. After performing

radical surgery, one of us (G. V. S.) is always left with a feeling of dissatisfaction because the anatomy of the pelvis makes a true "bloc" resection impossible. It might be argued that pelvic metastases can be eliminated only by surgery. Although irradiation has not been proved capable of destroying pelvic metastases, the greater total salvage in consecutive cases coincident with the increased use of radium and x-rays is circumstantial evidence that it may do so.

Of necessity one must resort to the radical operation in instances of operable, radioresistant cancers. There was only one such in this series so far as we could determine. At the Free Hospital for Women the radical operation is still occasionally performed, because it is requested, for purposes of instruction, perhaps unconsciously as an exercise of surgical prowess, as a reaction to a run of irradiation complications or because other pelvic tumors, inflammation or endometriosis make it preferable to radiation. In cases of very early cancer, viz., where the diagnosis is equivocal until biopsy, simple complete hysterectomy is likely to be performed to avoid radiation complications, with the exception of endocervical tumors, which so often are more advanced than apparent from examination. In some of those very early cases we have found less than the usual amounts of radium safe and curative, both with and without x-rays, but this procedure leaves a feeling of uncertainty. The facts derived from the above series again lead to the conclusion that for the great majority of patients the best treatment is a combination of radium and x-rays given in maximum relatively safe amounts, even at the cost of a small number of deaths and a large incidence of complications.

Summary

Eleven hundred and eleven consecutive, previously untreated, pathologically confirmable cases of cancer of the uterine cervix are reviewed. The percentages of patients who were alive five years after first treatment are as follows: 1902 to 1913, 12; 1914 to 1918, 19; 1919 to 1923, 23; 1924 to 1928, 28; 1929 to 1933, 38; 1934 to 1938, 43. The percentages of patients alive at ten years in the same groups to 1934 are: 7, 11, 12, 21, and 29. The percentages of patients alive at fifteen years to 1929 are: 7, 9, 8, and 15. The improved results are due for the most part to the use of radium and x-rays. Seventy-one per cent of the patients alive five years after treatment were alive at ten years, and 75 per cent of those alive at ten years were alive at fifteen years.

Two patients had proved recurrence between thirteen and fourteen years after irradiation.

Deaths, early and late, from treatment and intercurrent disease are listed. Complications and their treatment are given considerable attention, since they are such an important part of radiation therapy.

Four patients had another primary cancer at the time that of the cervix was treated and six later developed primary malignancies, two of which occurred in organs previously irradiated, namely, bladder and rectum.

Of the whole series of 1,111 patients, 5.2 per cent had had a previous supravaginal hysterectomy and 2.7 per cent more had had tubes or ovaries or both removed or tubal ligation.

References

1. Smith, George Van S., and Pemberton, Frank A.: *Carcinoma of the Uterine Cervix. The Results of Treatment Through 1933, Showing the Value of Supplementary X-Radiation*, New England, J. Med. 222: 481, 1940.
2. Bonney, Victor: *The Results of 500 Cases of Wertheim's Operation for Carcinoma of the Cervix*, J. Obst. & Gynae. Brit. Emp. 48: 421, 1941.

A TRANSPLANTABLE RAT TUMOR*

RUTH M. WATTS, PH.D., AND FRED L. ADAIR, M.D., CHICAGO, ILL.

(From the Department of Obstetrics and Gynecology, The University of Chicago)

IN VIEW of the relationship of hormones to tumor formation and its bearing upon clinical problems, it seems worth while to report the occurrence of a transplantable rat tumor arising in a colony of ovariectomized rats used for the assay of estrogens. Although there is no direct evidence that the tumor arose as the result of the administration of estrogen, this possibility is supported by the higher incidence of tumors and tumorlike growths in this colony than in the stock colony. The use of estrogen in this colony varied from the procedure commonly employed in producing tumors experimentally in that the estrogen was administered in physiologic doses intermittently over a long period rather than in a high dosage or by continuous treatment. According to Lipschütz the factor of timing is important in the production of tumors with estrogens. Much of the work on the relation of estrogens to tumor development has been concerned with mammary and connective tissue tumors, and often large doses of estrogens have been given for prolonged periods. The occurrence of spontaneous tumors in rats has been reviewed by Curtis, Bullock, and Dunning,¹ McEuen,² Ratcliffe,³ Jenney,⁴ and others. Various rat sarcomas have been found to be transplantable. McEuen⁵ has reported the occurrence of cancer in rats treated with estrone and has transplanted a spindle-cell tumor through 15 generations.

Our transplantable tumor is a sarcoma. It arose in the mesentery, but not in the usual site of the lymphosarcomas of the lymph nodes at the ileocecal junction. It was readily transplanted by transfer of a fragment of tissue or by the inoculation of a suspension of tissue and has been carried through 24 generations. It showed a high incidence of successful transfer. The transplanted tumor grew rapidly and more than half of the hosts failed to survive thirty days.

This work was undertaken not only because of our general interest in the field of the relationship of hormones to tumor formation⁶⁻⁸ but also in hope that an ovarian tumor might be induced which could be used to further our study on the relation of hormones to ovarian tumors.⁶

History of Rat Colony and Tumor Incidence

Stock Colony.—The colony of rats in which this tumor arose and with which it was continued was a Wistar strain which had been carried on in this laboratory since 1930 without interbreeding with other strains. The diet consisted of a modified Steenbock diet supplemented with bread, milk, ground beef, and lettuce, but later the stock rats received calf meal.

Assay Colony of Ovariectomized Rats.—A colony of adult ovariectomized rats was maintained for the purpose of assaying estrogens in

*This work has been done under a grant from the Douglas Smith Foundation for Medical Research of the University of Chicago.

the course of other investigations on the methods of assay of estrogens, excretion of estrogens in toxemia of pregnancy,⁹ and occurrence of estrogens in ovarian cyst fluids.^{6, 7} During the period 1934 to 1941 there was a total of more than 800 rats in this group. At the time of castration these rats weighed, on the average, 160 grams. Protocols on these animals include the dosage and preparations administered, dates of injection, response, and disposal of the animal. These rats received crystalline estrone, extracts of pregnancy urine and ovarian cyst fluids, usually administered subcutaneously in olive oil but occasionally as aqueous preparations. The rats received physiologic doses of these substances. After a positive response an animal was not used again for two weeks; after a negative response it was used the following week; after two negative responses it was given a priming dose of approximately 2 rat units of estrogen (pregnancy urine extract). Assay rats were used for about one year. As rats became irresponsive or old the assay colony was replenished with young rats. When the need for the colony diminished the last group was retained longer than usual. In this final group three malignant-appearing tumors were found. These will be discussed later.

Tumor Incidence.—In reviewing the disposal records of the breeding and stock colony, 32 instances (2.8 per cent) of tumors were recorded in 1,144 records. Of these, 18 (56.3 per cent) were mammary tumors and 4 (12.5 per cent) were intraperitoneal tumors. None was similar to the transplantable tumor which is the subject of this report.

In reviewing the protocols of the entire assay colony it was noted that of the 743 with autopsy records, 47 (6.3 per cent) had developed tumors or tumorlike growths. These were as follows: 14 subcutaneous at the injection site, 10 in the region of the neck, 8 intraperitoneal, 4 kidney, 2 vaginal, 1 each, mammary, adrenal, and thoracic cavity, 5 gastrointestinal tract, and 1 "oil cyst."

The subcutaneous growths appeared usually as lumps at the injection site and were sometimes associated with small "oil cysts." They were either cystic, firm fibrous tissue or friable malignant-appearing tissue. They attained sizes as great as 4 by 5.5 by 6 cm. One of these tumors was transplanted (see Rat FP 013⁵ below). The intraperitoneal tumors were of a miscellaneous nature. One of these (Rat FP 03⁸) is the subject of this report and one other (Rat FP 0456⁴) is described below.

The incidence of pathology was somewhat higher than in the stock colony. At no time was there any evidence in either colony of tumors of a parasitic or infectious origin, and no spontaneous sarcomas were observed such as described by McEuen⁵ and Jenney.⁴

Transplantation of Tumors.—One tumor in a stock rat and three tumors arising in this assay colony of ovariectomized rats appeared to be malignant and were tested by transplantation.

Rat FP 03⁸.—The tumor arising in the mesentery of this ovariectomized rat is the subject of this report and will be discussed in detail. The tumor was easily transplanted and was transferred through 24 generations within twenty-seven months.

Rat FP 0156⁴.—This ovariectomized rat had two subcutaneous cysts on the back in the region of the injection site, and a tumor approximately 1 by 2 by 4 cm. adjacent to, and partially obliterating, the caudate lobe of the liver. Both the liver tumor and the subcutaneous tumor resembled in every way the tumors observed from the transfer of the tumor found in Rat FP 03⁸. Twenty-two milliliters of ascitic fluid were obtained. The liver tumor was transferred by the emulsion technique through three generations but the one tumor transferred to the fourth generation failed to "take." The tissue resembled a sarcoma.

Rat FP 013⁵ was an assay rat with a subcutaneous tumor 1 by 2 by 2 cm. This tumor was composed of numerous locules, some of which contained a milky fluid. The tissue varied from nodular firm tissue to

friable hemorrhagic tissue and appeared to be malignant. Microscopically it resembled the sarcoma of Rat FP 03^s and the tumor of Rat FP 0456⁴. Three transfers of this tumor were not successful.

Rat FP 25¹³ was a female rat from the breeding colony. The tumor arose in the vagina and microscopically it did not resemble the tumors which appeared in the assay rats. All three of the primary transfers were successful but 16 transfers in the second generation failed.

Description of Tumor

History of Host.—A normal young adult rat, FP 03^s, was bilaterally ovariectomized, and after twelve days estrogen injections were begun. Within the next seventy-two weeks the rat received 51 injections of estrogen in oil; of these, 11 were crystalline estrone, 23 pregnancy urine, 17 "priming doses" of pregnancy urine extract, and one an extract of ovarian cyst fluid. Twenty-four extracts gave positive responses and 27 negative. Injections were such that a positive response was obtained every second or third week. Two weeks after the last injection the rat was sacrificed because of a large tumor distending the abdomen.

Gross Description.—The tumor arose in the mesentery and invaded the intestinal wall. It did not arise in the lymph nodes at the ileocecal junction. The tumor measured 5 by 5 by 5 cm. It was irregular in shape and showed cystic structures two of which contained 37 ml. and 45 ml. of watery fluid, respectively. Some of the solid portions were hemorrhagic friable tissue and others pale yellow friable tissue which was somewhat translucent.

Microscopic Description of Original.—Fig. 1 is a photomicrograph (x370) of the portion of the tumor from which tissue was taken for the original transfers. The cellular structure is uniform and resembles a round-cell sarcoma. The cells stain deeply with hematoxylin and eosin stain and often show many stages of mitotic division. There is a characteristic tendency for a rosettelike arrangement of the cells. Fig. 2 is the same microscopic section as shown in Fig. 1 but at x450 magnification. While the exact character of the tumor may be questioned, morphologically it appears to be a sarcoma.

Microscopic Examination of Transferred Tumor.—More than 160 microscopic examinations have been made of transferred tumor tissue, representing tumors in various sites and in the eleven lines carried on from the original tumor. All lines were similar. Irrespective of the site of the tumor, the tissue characteristics remained constant through 24 generations. Neither variations in the cell picture nor any tendency to change of type were observed. The tissues were fixed in Zenker's solution and stained with hematoxylin and eosin. Tumor Line 2 was followed microscopically in 24 generations. The photomicrographs of the original tumor are shown in Figs. 1 and 2; the tenth generation and the twentieth generation of Line 2 are shown in Figs. 3 and 4, respectively.

Transplantability.—It was possible to transfer this tumor by implantation of fragments of tissue or by the injection of a suspension of tissue. This was accomplished either subcutaneously or intraperitoneally. The tumor was carried on in eleven lines: three lines were followed for 10 generations, one for 12, one for 17, one for 19, two for 21, two for 22, and one for 24. The tissue characteristics remained the same, but the ease of transfer increased with repeated transfers. No line died out spontaneously and no regression of the tumor was ever observed. There was no evidence that the tumor was infectious in nature and it never appeared elsewhere in the colony. Cultures of the tumor tissue were negative and the tumor was transmitted only by inoculation or transplantation of tissue. The tumor invaded other tissues but there were no proved instances of metastases. However, more than half of the hosts died within less than thirty days after receiving a transfer of the tumor tissue.

Bacteriologic Examination

In order to rule out the possibility of an infectious nature of the tumor and the subsequent transmission in this way, bacteriologic examinations* have been made of the tumor tissue. Fifteen tumor hosts

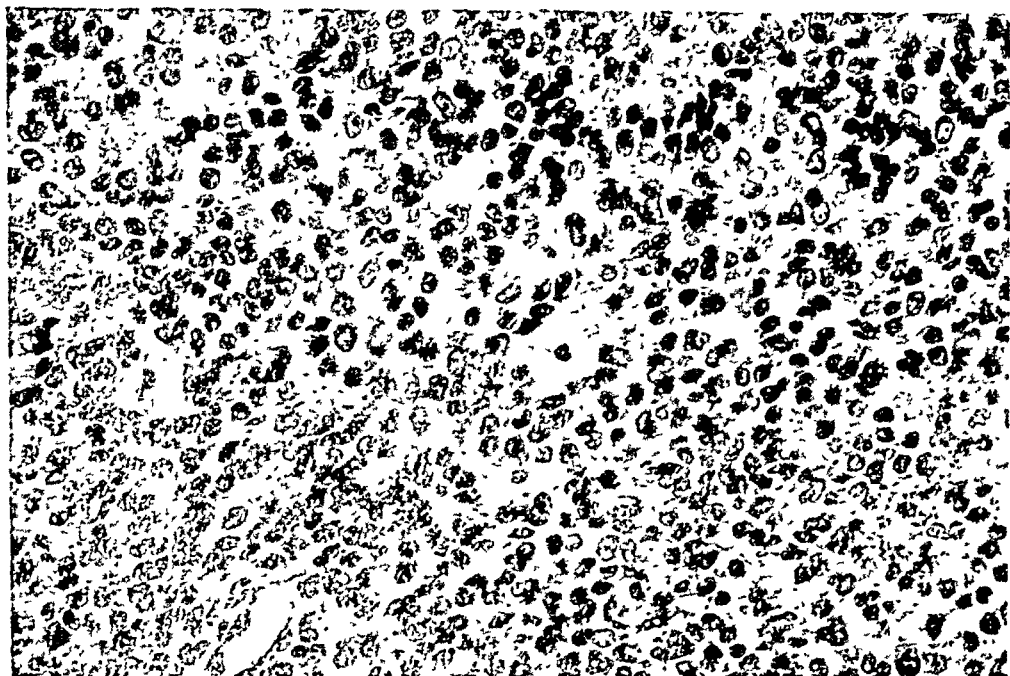


Fig. 1.—Original tumor from the mesentery of Rat MP 033. ($\times 370$.)

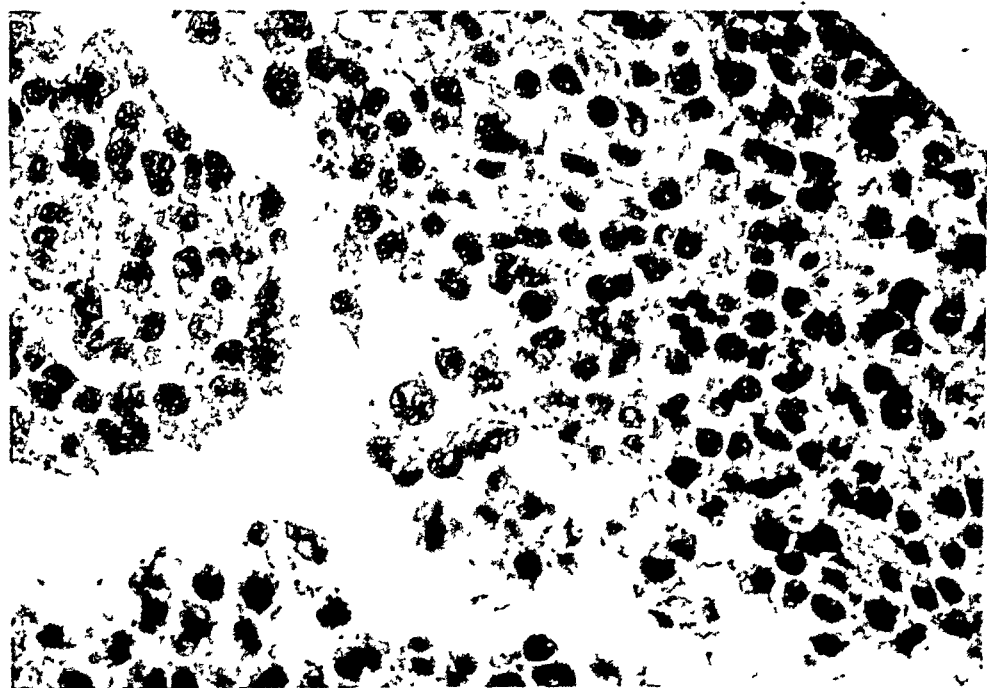


Fig. 2.—Original tumor from the mesentery of Rat MP 033. Same microscope section as shown in Fig. 1. ($\times 150$.)

have been examined. Twenty-three examinations were made of the tumor tissue from tumors in various states of development or from different parts of the same tumor. Nine specimens of ascitic fluid were examined. The ages of the tumors, as represented by the time elapsing after the transfer of the tumor tissue to the host, were 8, 8, 13, 17, 20,

*We are indebted to Dr. Lucille Hae for these examinations.

24, 29, 30, 31, 45, and 49 days. The generations represented were 11, 14, 15, 16, 17, 18, 20, and 21. No organisms were found in direct smears made from the tumor tissue or the ascitic fluid and stained with Gram's or acid-fast stains. Cultures made on blood agar plates and in Rosenow's brain broth medium showed no growth.

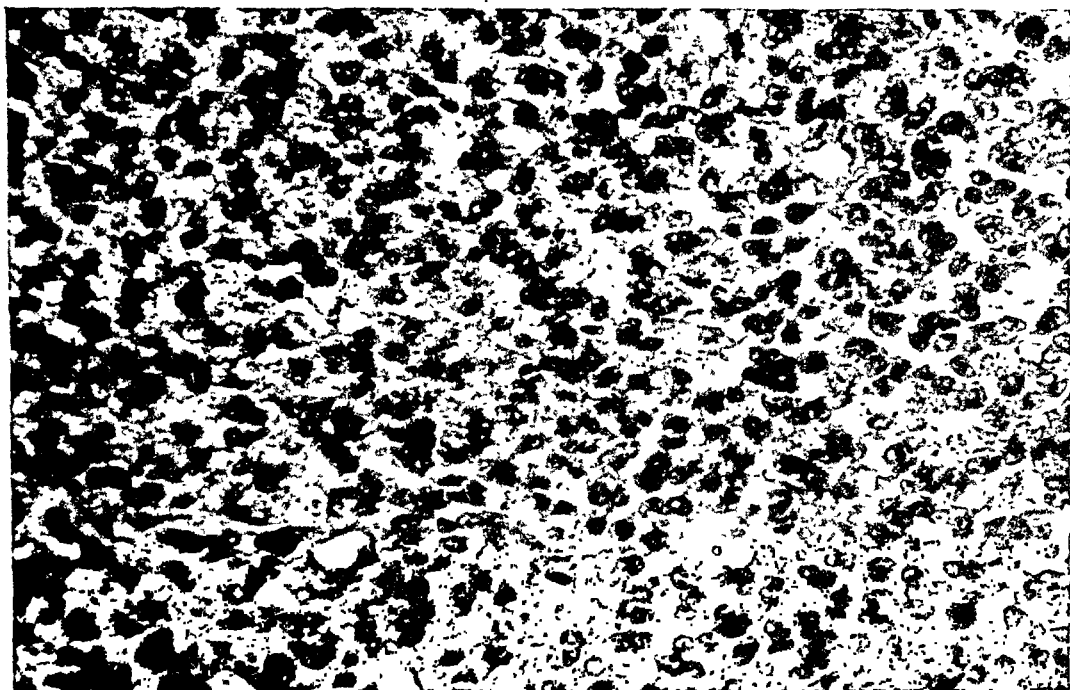


Fig. 3.—Peritoneal implant in Rat MP 347 twenty-eight days after transfer. Generation 10 of Line 2. ($\times 335$.)

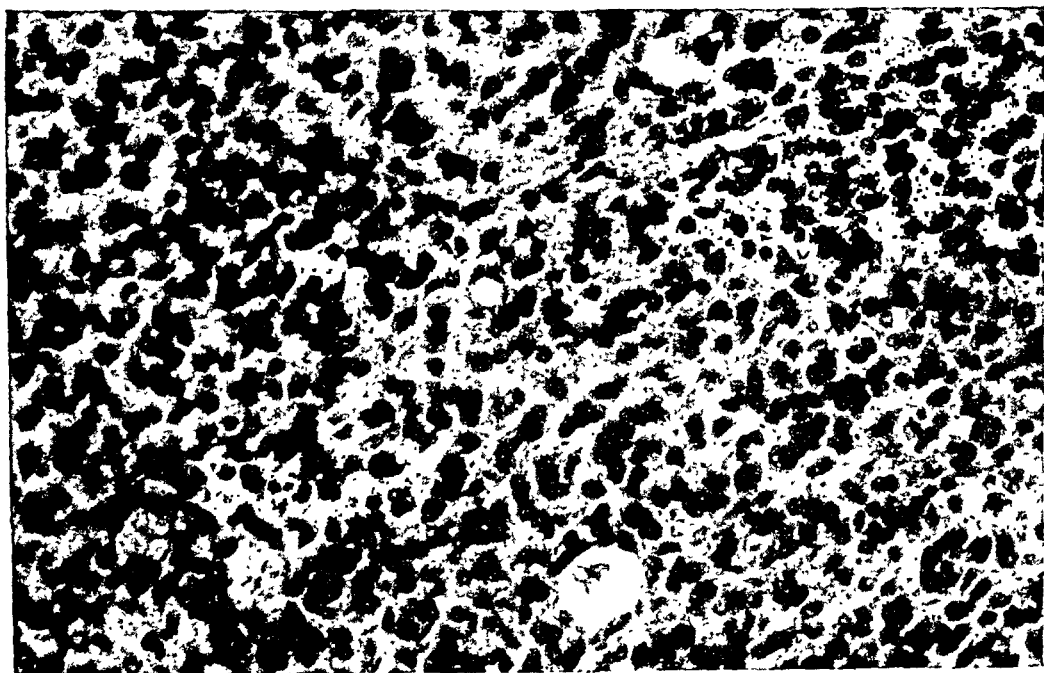


Fig. 4.—Omental tumor in Rat MP 136² twenty-two days after transfer. Generation 20 of Line 2. ($\times 335$.)

Filtrates From Tumor Tissue

In studying the nature of the transmission of the tumor, filtrates were made from the tumor tissue. In the first experiment a suspension of an omental tumor was used and the filtrate prepared by filtration through a Berkefeld filter "V." Three rats received filtrate equivalent

to 200 mg. of tissue and showed no evidence of tumor growth at autopsy. In control groups, all three rats receiving 200 mg. of tissue, two of three rats receiving 100 mg., and two of three rats receiving 25 mg. developed tumors. Three of four rats which received tissue suspension equivalent to 100 mg. of tissue, but which was incubated for five hours at room temperature, developed tumors also.

In the second experiment a filtrate of a tumor enveloping the caudate lobe of the liver was prepared by filtration of a suspension of tissue through a Pyrex sintered glass filter ("fine"). One rat received an amount of filtrate equivalent to 50 mg. of tissue and one an amount equivalent to 100 mg. of tissue; both failed to develop tumors. Three of the four controls which received 100 mg. of tissue developed tumors.

In the third experiment the filtrate was made from an omental tumor by filtration through a "fine" Pyrex sintered glass filter. The four rats receiving 100 mg. of tissue developed tumors, but 3 receiving filtrate equivalent to that amount of tissue were all negative.

In the fourth experiment the filtrate was obtained by passing a suspension of an omental tumor through a Berkefeld filter "V." Three pairs of control rats received amounts of tissue suspension containing 10, 25, and 100 mg. of tissue, respectively, and all developed tumors. Two rats received filtrate equivalent to 100 mg. and two equivalent to 200 mg. of tissue, and these were all negative.

Since no tumors developed from either of these filtrates, it would seem that the factor producing these tumors was not present in a sterile filtrate obtained from Berkefeld filtration or in a cell-free, nonsterile filtrate passed through the sintered glass filter.

Techniques of Transfer

Hosts.—The hosts were selected with respect to sex, weight, and age. In routine transfer of the tumor three adult hosts were used.

Tissue Transfer Method.—The first transfers of the tumor were made by implantation of small fragments of tissue, approximately 2 by 2 by 2 mm. The transfers were made either by implanting subcutaneously or by embedding in the ovarian fat using sterile technique. This method was employed only in the early work.

Tissue Suspension Method.—A weighed amount of tissue was macerated with fine-tipped surgical scissors, using aseptic conditions, until it would pass through a No. 19 hypodermic needle. This macerated tissue was suspended in a known amount of physiologic saline solution so that 1 or 2 ml. of suspension contained the required amount of tissue to be inoculated. The amount of tissue transferred varied, and amounts as low as 0.5 mg. were used. In the routine transfers, 100 mg. of tissue were used. This amount was undoubtedly excessively large but since this amount was adopted as a standard procedure early in the investigation, it was continued for uniformity. Transfers were usually not made until the host died or was sacrificed because of a terminal condition.

Incidence of Successful Transfer

The incidence of successful transfer of the transplanted tumor is shown in Table I. The data have been compiled in regard to the sex but not the age of the host, and as to whether or not a weighed amount of tissue was transferred. In early work the tissue transferred was not weighed, but the amounts were comparable to those used later. In general, the hosts were adult, and three rats were used for each tissue transfer. The transfers were all made by intraperitoneal injection of a sus-

pension of tissue as described above. Of the 1,171 transfers, 839 (71.7 per cent) were successful, irrespective of the amount of tissue inoculated. Of the 764 transfers made to male hosts, 550 (72.0 per cent) were successful, and of the 407 transfers made to female hosts, 289 (71.0 per cent) were successful. In the group in which transfers were made with weighed tissue, 444 (76.4 per cent) of the 581 males and 195 (73.9 per cent) of the 264 females developed tumors. In routine transfer of the tumor, 100 mg. of tissue were transferred. These data appear also in Table I. Three hundred and fifty-three (81.0 per cent) of the 436 transfers were successful. Of the 318 male hosts, 257 (80.8 per cent), and of the 118 female hosts, 96 (81.4 per cent) developed tumor. These data form the basis for Table II, but the incidence of "takes" differs slightly because only hosts allowed to survive at least thirty days are included, and hosts receiving three tissues which gave entirely negative responses are excluded. The data for males are based on 105 tumor tissues and for the females on 44 tissues. The data indicate that there is no sex difference in respect to the incidence of successful transfers.

TABLE I. INCIDENCE OF SUCCESSFUL TRANSFERS

TUMOR TISSUE		MALES				FEMALES			TOTAL		
TRANSFERS	NO.	NO.	NO. %		NO.	NO. %		NO.	NO. %		
			POSITIVE	POSITIVE		POSITIVE	POSITIVE		POSITIVE	POSITIVE	
Amount weighed	181	581	444	76.4	264	195	73.9	845	639	75.6	
Amount not weighed	113	183	106	57.9	143	94	65.7	326	200	61.3	
Total	294	764	550	72.0	407	289	71.0	1,171	839	71.7	
100 mg.	137	318	257	80.8	118	96	81.4	436	353	81.0	

TABLE II. SURVIVAL PERIOD OF HOSTS RECEIVING 100 MG. OF TUMOR

	MALE HOSTS			FEMALE HOSTS			TOTAL GROUP		
	NO.	%	% OF POSITIVE GROUP	NO.	%	% OF POSITIVE GROUP	NO.	%	% OF POSITIVE GROUP
POSITIVE TRANSFERS									
Survival Period									
0-19 days	31	11.4	13.5	12	10.9	13.6	43	11.2	13.5
20-29 days	101	37.0	43.9	35	31.8	39.8	136	35.5	42.8
30 or more days	98	35.9	42.6	41	37.3	46.6	139	36.3	43.7
Total	230	84.3	100.0	88	80.0	100.0	318	83.0	100.0
NEGATIVE TRANSFERS	43	15.7		22	20.0		65	17.0	
TOTAL	273	100.0		110	100.0		383	100.0	

Survival Period of Tumor Hosts

The survival period of tumor-bearing rats is shown in Table II. In this group, 383 rats received intraperitoneal inoculations of 100 mg. of tumor tissue and were allowed to survive at least thirty days. Of this group, 318 rats (83.0 per cent) showed successful transfers. Of the 273 transfers made to male hosts, 230 (84.3 per cent) were successful, and of the 110 transfers made to female hosts, 88 (80.0 per cent) were successful. These transfers were made from 127 tumors; three tissues which did not "take" have been omitted. Of the entire group of 383 hosts, 43 (11.2 per cent) survived less than twenty days after inoculation with tumor tissue, 136 hosts (35.5 per cent) survived between twenty and twenty-nine days, 139 hosts (36.3 per cent) survived longer than thirty days, and 65 hosts (17 per cent) were negative. The survival period has been determined by the death of the host or by a terminal condition necessitating sacrificing the animal.

In the group of 318 successful transfers, 43 hosts (13.5 per cent) survived less than twenty days, 136 hosts (42.8 per cent) survived

twenty to twenty-nine days, and 139 hosts (43.7 per cent) survived more than thirty days. The survival period is dependent not only upon the extent and involvements of the tumor but also upon the location and character of the tumor and the ease with which it ruptured causing extravasation of blood and exsanguination of the host.

Sites of Tumor Development

In determining the incidence of the sites of tumor development, a group of 179 hosts surviving less than thirty days has been used. This is the same group that appears in Table II. The hosts all received intraperitoneal inoculations of a suspension of 100 mg. of tumor tissue. One hundred and twenty-seven tumors were transferred. The tumors which were transferred occurred in the following sites: omentum 76, liver site 25, mesentery 14, genital fat 7, diaphragm 2, peritoneal implant 1, thoracic cavity 1, region of the kidney 1. The microscopic appearance of the tissue was the same regardless of the site of the tumor.

TABLE III. INCIDENCE OF SITES OF TUMORS IN HOSTS SURVIVING LESS THAN THIRTY DAYS

TUMOR SITES	NO. OF TUMORS IN HOSTS SURVIVING		INCIDENCE	
	LESS THAN 20 DAYS	20-29 days	TOTAL NO. OF TUMORS	IN HOSTS %
Omentum	43	133	176	98.3
Liver site	40	131	171	95.5
Genital fat	40	116	156	87.2
Mesentery	36	113	149	83.2
Implants				
Peritoneum	33	95	128	71.5
Xiphoid process	18	52	70	39.1
Diaphragm	24	67	91	50.8
Subcutaneous	13	40	53	29.6
Intestinal tract	6	17	23	12.8
Kidney region	2	6	8	4.5
Kidney	0	6	6	3.4
Spleen	0	4	4	2.2
Thoracic cavity	0	3	3	1.7
Stomach	0	1	1	0.6
Total number of sites	255	784	1,039	
NUMBER OF HOSTS	43	136	179	

The various sites where tumors developed are enumerated in Table III and include the omentum, liver site (liver and regions adjacent) genital fat, mesentery, intestinal tract, kidney, spleen, stomach, diaphragm, implants on the peritoneal wall, implants over the xiphoid process, along the back near the kidney, thoracic cavity and subcutaneous tissue. According to this classification, 1039 tumor sites were observed in the 179 hosts which failed to survive thirty days. The incidence of tumors in these various sites is shown in Table III. The highest incidence is in the omentum: 176 of 179 hosts (98.3 per cent) developed omental tumors. Tumors of the liver, around the liver, or growing between the lobes were found in 171 hosts (95.5 per cent). One hundred and fifty-six hosts (87.2 per cent) were found to have tumors involving or replacing the fat associated with the genital organs. Sites other than those listed have been observed, but with amounts of inoculated tissue other than 100 mg. Among those tumors were tumors of the ovary, testis, uterus, seminal vesicle, thymus, lymph nodes, heart, and lung.

The incidence of the number of different sites in which the tumors developed is shown in Table IV. The greatest number of different sites observed in one host was ten. The highest incidence was shown for seven sites. Twenty-six and three-tenths per cent of the hosts showed tumors in seven sites; 87.1 per cent showed tumors in four to eight sites; 89.9 per cent had tumors in more than three sites.

TABLE IV. INCIDENCE OF NUMBER OF SITES OF TUMOR IN HOSTS RECEIVING 100 MG. TISSUE AND SURVIVING LESS THAN THIRTY DAYS

NO. OF SITES	INCIDENCE	
	NO. OF HOSTS	%
1	3	1.7
2	3	1.7
3	12	6.7
4	23	12.8
5	27	15.1
6	40	22.3
7	47	26.3
8	19	10.6
9	4	2.2
10	1	0.6
Total	179	100.0

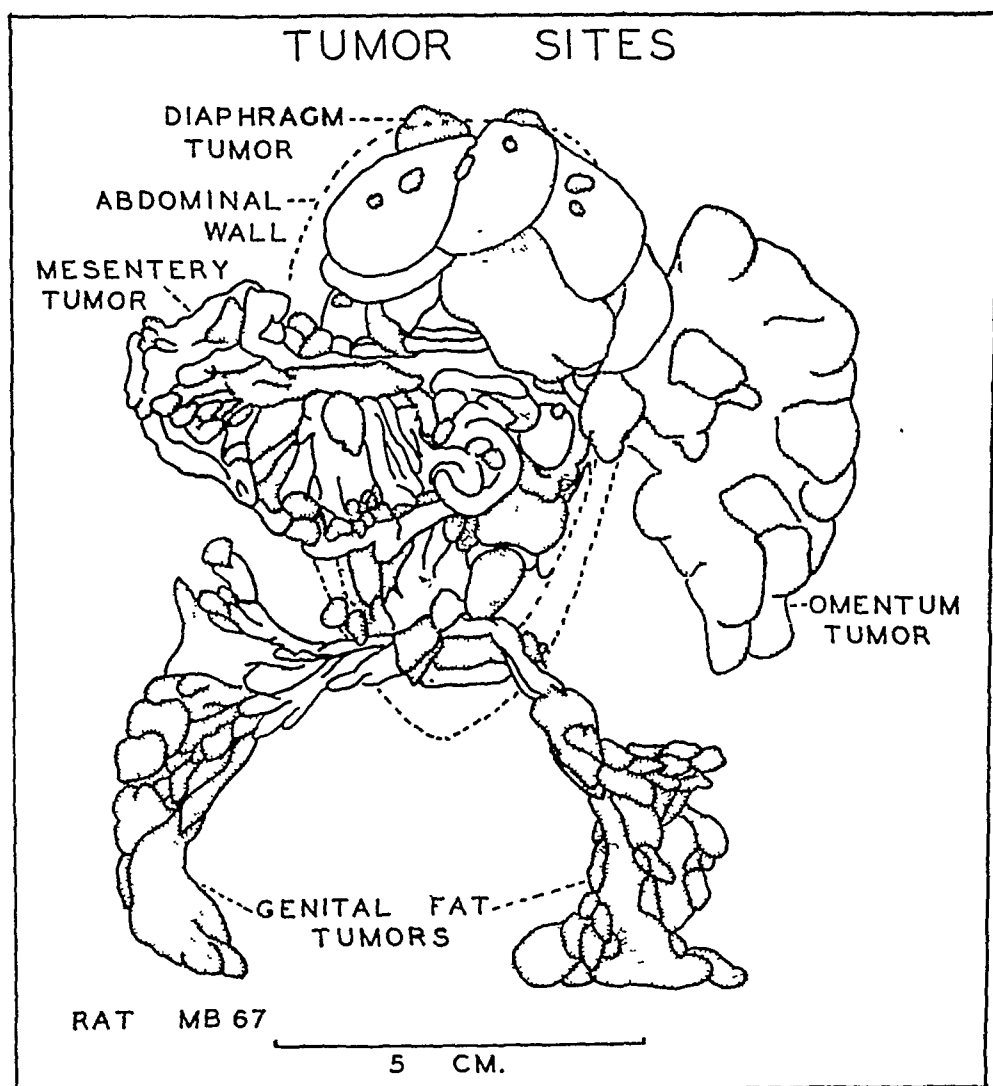


Fig. 5.—Sites of tumor formation. Drawing of Rat MP 67 twenty-one days after intraperitoneal transfer of a suspension of tumor tissue. Tumors are represented by shaded areas.

The sites of the tumor development are illustrated in the drawing of Rat MB 67, Fig. 5. This rat was sacrificed twenty-one days after inoculation because of a terminal condition. The abdominal cavity was distended with tumors and there was 10 ml. of blood-tinged ascitic fluid. There was a large tumor of the omentum, composed of nodules which had fused. The genital fat was almost completely replaced by tumors. There were numerous tumors throughout the mesentery. The liver was studded with small implants and one lobe of the liver was obliterated. The tumor on the diaphragm had penetrated and was growing in the thoracic cavity. There were many implants on the peritoneal

wall (not shown) and on the kidney. This illustrates the extensive involvement commonly observed when transfers are made by intraperitoneal inoculation of a suspension of tissue cells.

Effect of the Amount of Tissue Transferred Upon the Success of Transfer

Although most of the transfers were made with 100 mg. of tissue, adopted as standard procedure, smaller amounts have been transferred successfully. The effect of the amount of tissue transferred upon the success of the transfer is shown in Table V. These are the same data as appear in Table I. Four hundred and thirty-six rats received transfers of 100 mg. of tissue and 237 received tissue in the amounts of 0.5, 0.8, 1, 2, 5, 10, 25, 40, and 50 mg. When differing amounts of tissue were used, the percentage of "takes" varied between 61.1 and 100. Hosts receiving 5 mg. of tissue or less showed 74.2 per cent of "takes," those with 10 to 40 mg., 65.9 per cent, and those with either 50 or 100 mg., 81.0 per cent. The entire group receiving 40 mg. or less showed a lower percentage of "takes" than the groups with 50 and 100 mg., but there seem to be no trends within that former group.

TABLE V. EFFECT OF AMOUNT OF TISSUE TRANSFERRED UPON THE SUCCESS OF TRANSFER

TRANSFERS			HOSTS	
AMOUNT OF TUMOR (MG.)	NO. OF TISSUES	NO.	NO. POSITIVE	% POSITIVE
0.5	9	16	11	68.8
0.8	1	5	5	100.0
1	9	22	14	63.6
2	2	6	5	83.3
5	7	17	14	82.4
10	13	36	22	61.1
20	10	33	21	63.6
25	8	19	14	73.7
30	1	2	2	100.0
40	10	39	26	66.7
50	4	42	34	81.0
100	137	436	353	81.0

Increase in the Transplantability of the Tumor

If these data presented above are summarized, using only transfers in which three hosts were used for each tissue, 93 groups of males and 28 groups of females are obtained. The male hosts have been divided into three chronological groups of 31 groups of three hosts each. In the earliest group (Group I) 10 of the 31 groups (32.3 per cent) showed all three of the transfers successful in each group, in the intermediate group (Group II) 51.6 per cent, and in the last group (Group III) 74.2 per cent. In the remaining groups some transfers in each group of three were negative. The percentage of successful "takes" for Group I was 72 (67 of 93 transfers), for Group II, 79.6 (74 of 93 transfers), and for Group III, 90.3 (84 of 93 transfers). These data seem to indicate an increase in the ease of transplantability with repeated transfer of the tumor. During the entire period 49 (52.7 per cent) of the 93 groups showed three successful transfers in each group of three hosts, and 225 (80.6 per cent) of the 279 transfers were successful. During the same period 28 groups of three females each received transfers of tumor tissue. Seventeen (60.7 per cent) of the 28 groups of three showed all three transfers of each group successful, and 67 (79.8 per cent) of the 84 transfers. The males received transfers from 92 tissues and the females from 28 tissues, usually the same tissues as received by the male hosts. These data appear in Table VI.

TABLE VI. INCREASE IN THE TRANSPLANTABILITY OF THE TUMOR

HOSTS	NO. OF TIS- SUES	NO. OF HOSTS	NO. OF GROUPS OF 3	GROUPS ALL POSITIVE		GROUPS POSITIVE AND NEGATIVE		TOTAL TRANSFERS	
				NO.	%	NO.	%	NO. POSITIVE	% POSITIVE
Male Hosts									
Group I	30	93	31	10	32.3	21	67.7	67	72.0
Group II	31	93	31	16	51.6	15	48.4	74	79.6
Group III	31	93	31	23	74.2	8	25.8	84	90.3
Total	92	279	93	49	52.7	44	47.3	225	80.6
Female Hosts	28	84	28	17	60.7	11	39.3	67	79.8

Course of the Tumor Development

In order to study the mode of transmission and the rate of growth of the transplanted tumors, transfers have been made to a group of rats and four or five rats have been sacrificed at various time intervals. Three such groups were inoculated for this purpose.

Experiment 1.—Four groups of five male rats weighing 205 ± 5 grams were used as hosts. Each host received an intraperitoneal inoculation of 2 ml. of a suspension of tumor tissue equivalent to 100 mg. of tumor. The tumor used was characteristic soft friable tissue from an omental tumor of the thirteenth generation obtained 103 days after inoculation.

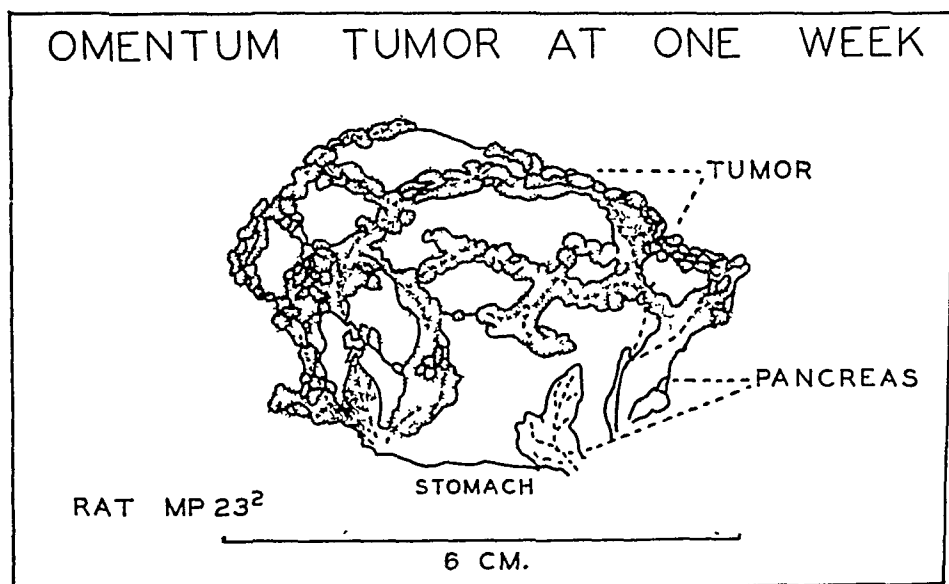


Fig. 6.—Drawing of an omental tumor in Rat MP 23² seven days after intraperitoneal transfer of a suspension of tumor tissue. Shaded areas show early tumor and the plain areas the connecting membrane of the omentum.

Development at 7 days: Five rats were sacrificed on the seventh day after inoculation. All showed definite tumor development in the omentum in the form of small nodules which followed the blood supply, giving the tissue a lacelike appearance. This is illustrated by the drawing of Rat MP 23² (Fig. 6). The omental tumor measured 4 by 6 cm. and was composed of 1 to 3 mm. nodules along the blood vessels, held together by the very thin sac of the omentum. The nodules were firm pale tissue. There was also a tumor in the genital fat. The omental tumor of Rat MP 24² was less extensive than that of Rat MP 23² but there was a 5 mm. tumor over the xiphoid process which was of a more advanced stage and was hemorrhagic. The omental tumor of Rat MP 25² was similar to but showed fewer nodules than Rat MP 23²; there was a 5 mm. tumor in the genital fat; the membrane over the caudate lobe of the liver had several beginning tumors. The omental tumor of Rat MP 26² differed from that of Rat MP 23² in that the nodules com-

prising it were larger and firmer and the growth extended to the membrane surrounding the spleen and adjoining the stomach. A tumor was present in the mesentery. In Rat MP 27² the omental tumor was similar to Rat MP 23² but the membrane surrounding the caudate lobe of the liver was extensively involved. There was no evidence of an inflammatory process in any of these rats.

Development at 14 days: In the group of five rats sacrificed at the end of 14 days, two were negative. The tumors of the other three were similar to those of the previous week but showed more advanced development and a small amount of ascitic fluid. In Rat MP 28² the omental tumor was composed of nodules 1 to 5 mm. in diameter, and the larger nodules were soft friable pink tissue. Small tumors were found surrounding the spleen, on the spleen, in the genital fat, and at the injection site. The omental tumor of Rat MP 37² was less extensive and was composed of flat nodules; there was a 2 mm. tumor on the caudate lobe of the liver. Rat MP 38² showed rapid tumor growth. The firm nodules of the omental tumor were 1 to 8 mm. in diameter and gave a nodular rather than lacelike appearance to the tumor. The tumor growing around the spleen was advanced, consisting of soft hemorrhagic tumor tissue. There were peritoneal implants, implants on the liver, and two approximately 5 mm. tumors in the mesentery. The omental tumor was transferred to three male rats (approximately 260 grams). In spite of the relatively early development of the tumor, 100 mg. of the tissue produced extensive tumors in the hosts and they reached a terminal stage in 23, 28, and 41 days, respectively. They were distended with 64, 48, and 100 ml. of ascitic fluid, respectively. Extensive tumor formation was found in the omentum, mesentery, genital fat, liver site, peritoneal wall, and the diaphragm.

Development at 21 days: The five hosts sacrificed at 21 days after inoculation showed advanced and extensive tumor development, as illustrated by Rat MP 56² in Fig. 7. When the tumors were exposed, they were similar to those appearing in Rat MP 67 sacrificed at 21 days (See Fig. 5). A characteristic finding was a large quantity of ascitic fluid. Rat MP 56² had 37 ml. of ascitic fluid. The omental tumor measured 1 by 4.5 by 8 cm. and was composed of nodules 5 to 8 mm. in diameter. The omental membrane was not visible on the outside of the tumor. However, the tumor retained the sac formation. There were tumors under the liver and the caudate lobe was obliterated. There were many 5 mm. tumors in the genital fat and some in the mesentery. Rat MP 45² had an omental tumor similar to that of Rat MP 56² which measured 2 by 4.5 by 7.5 cm. and was comprised of nodules 5 to 10 mm. in diameter. The caudate lobe of the liver was replaced by tumor and the tumor growing under the liver measured 1 by 2 by 3 cm. The mesentery contained many 5 mm. tumors and the genital fat several. There was a 1 by 1 by 1.5 cm. implant at the injection site and the peritoneal wall was studded with small implants. There were 40 ml. of ascitic fluid. The tumor growth in Rat MP 46² was slight and there was no ascitic fluid. There were 5 mm. tumors in the omentum, beneath the caudate lobe of the liver, in the genital fat, and at the injection site. Rat MP 47² showed nothing striking. There were 28 ml. of ascitic fluid. The omental tumor was of typically nodular, soft, and hemorrhagic tissue, measured 1 by 3.5 by 4.5 cm., and was comprised of 5 to 15 mm. nodules. The caudate lobe of the liver was replaced by a tumor measuring 0.5 by 1.5 by 2.5 cm. There were implants and tumors in the genital fat. Rat MP 48² showed earlier development of the omental tumor but the nodules were composed of soft friable tissue and were 5 to 10 mm. in size. A more advanced hemorrhagic tumor, measuring 0.5 by 1 by 2.5 cm., was found beneath the spleen. The caudate lobe of the liver was almost completely replaced by tumor. There was a tumor in the genital fat and an implant at the injection site.

Development at 28 days: Of the five hosts sacrificed at 28 days, three were negative and no particular advancement was shown by the others. Rat MP 58² had an encapsulated tumor arising in the omentum which was attached to the genital fat. It measured 1 by 2 by 3 cm. At one point the capsule had ruptured and characteristic soft hemorrhagic tissue was being extruded. Tumors were growing in the membrane surrounding the caudate lobe and spleen. There were 6 ml. of ascitic fluid. Rat MP 78² had 15 ml. of ascitic fluid. The omental tumor was not extensive but was also attached to the genital fat. Two tumors approximately 2 cm. in diameter were growing under the liver. There were implants. The tumors in MP 123² were 5 to 15 mm. in diameter and were found in the omentum, mesentery, in the liver site, and on the peritoneum.

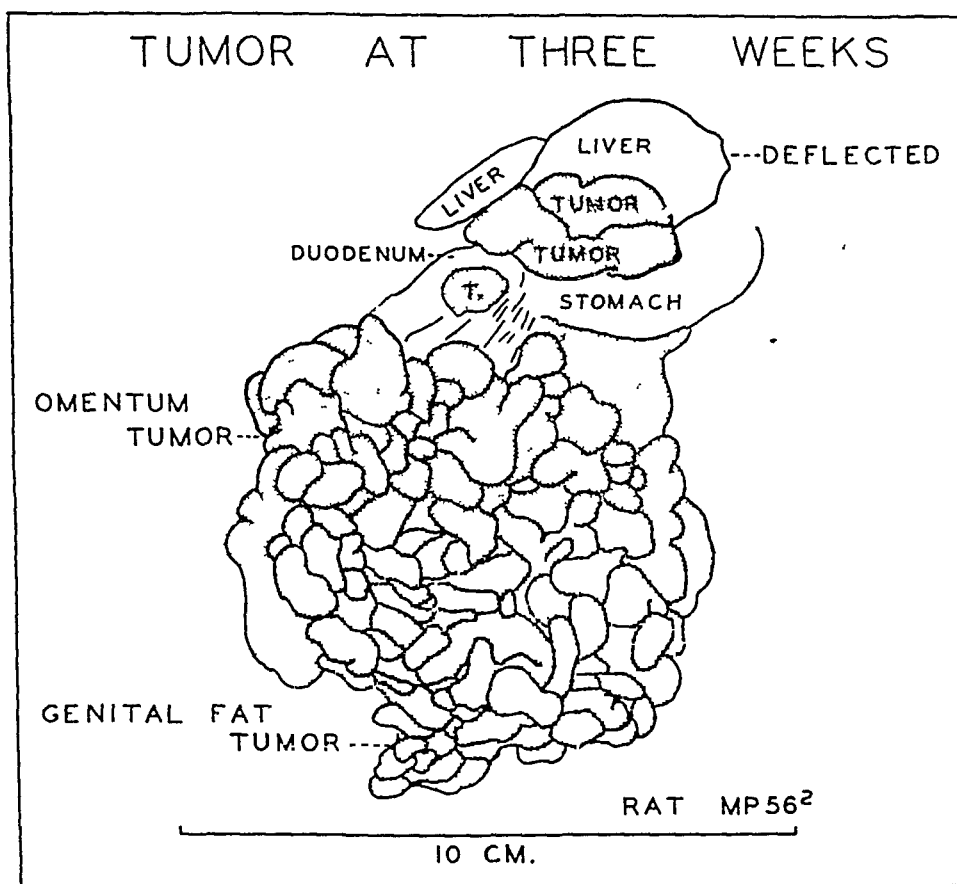


Fig. 7.—Drawing of Rat MP 56² twenty-one days after intraperitoneal transfer of a suspension of tumor tissue. Same experimental group as illustrated in Fig. 6.

Experiment 2.—This experiment was carried out to confirm the findings of Experiment 1. One hundred milligrams of a mesentery tumor in suspension were inoculated into 23 male rats weighing 205 to 260 grams. The tumor was of the fourteenth generation and was obtained 51 days after transfer. Groups of these hosts were sacrificed at 1, 2, 3, and 4 weeks and in general they confirm the findings of the previous experiment.

Development at 7 days: The five rats sacrificed at 7 days after inoculation resembled those of Experiment 1 and showed no deviations from the findings illustrated by Fig. 6. Tumors of the omentum, liver site, mesentery, and implants were found also.

Development at 14 days: In the group of five hosts sacrificed at 14 days, two showed no evidence of tumor formation except several tiny nodules. The other three showed more advanced development of the omental tumor than at the same period in Experiment 1. The omental tumor measured 5 cm. in each and was composed of tumor nodules which were firmer and more hemorrhagic. One omental tumor was encapsulated by a thin shiny membrane but on the inside the tumor was the usual friable tissue. Tumors were found in the liver site and on the

peritoneal wall but no tumors were present in the genital fat or in the mesentery.

Development at 21 days: Of the original group of five hosts to be sacrificed at 21 days, one was sacrificed at 18 days because of the terminal condition. A cystic and necrotic tumor was found growing on the posterior abdominal wall and obstructing the colon and bladder. The omental tumor measured 3.5 by 4 cm. and was comprised of nodules 5 to 15 mm. in size. Tumors were also found in the region of the caudate lobe of the liver, in the mesentery and genital fat, and on the peritoneum. At 21 days five hosts were sacrificed. All of these showed well-advanced but less extensively developed omental tumors than Rat MP 56², Fig. 7. Tumors were found also in the region of the liver, the genital fat, mesentery, and on the peritoneum. A third rat showed about a two-week development of the omental tumor, measuring 4.5 by 5 cm., and comprised of 5 mm. nodules. Other tumors were found in the genital fat, liver site, and peritoneum. A fourth rat showed advanced development with an omental tumor 1 by 4 by 5 cm., which was partly encapsulated. This had ruptured in several areas and characteristic friable tissue was being extruded. Other tumors were found in the mesentery, liver site, genital fat, peritoneum, and diaphragm. The fifth rat was in a terminal stage with very advanced tumors in all of the usual sites. The omental tumor measured 1 by 5 by 5 cm. and was composed of nodules 5 to 15 mm. in diameter and of varying degrees of tumor development. The tumor extended under the stomach and spleen and liver and entirely surrounded the caudate lobe. The genital fat was completely replaced by tumor. The peritoneum was studded with small implants, and tumors were found in the mesentery. The tumor growing on the diaphragm had perforated it and was extending into the thoracic cavity.

Development at 28 days: Of the five rats to have been autopsied at 28 days, one died on the eighteenth day and one was sacrificed on the twenty-sixth day after inoculation. The rat that died on the eighteenth day had an omental tumor, 2 by 4 by 5 cm., which was composed of hemorrhagic tumor tissue. There were numerous implants and tumors in the mesentery, genital fat, and liver site. The other host had an encapsulated omental tumor measuring 1 by 3 by 7 cm.; the tissue was typical. This tumor was connected to a 1.5 cm. tumor in the mesentery, to genital fat tumors, and to an extensive liver site tumor measuring 2 by 3.5 by 3.5 cm. which was growing on the median lobe and embedded in the caudate lobe. The third rat had been used to complete the group sacrificed at 21⁶ days. A fourth host had one encapsulated tumor (3 by 3.5 cm.) surrounding the cecum and another the colon. These were attached to the omentum which contained only a few tumor nodules. There were small tumors in all the usual sites. Three rats showed only scattered small tumors and nothing unusual.

Experiment 3.—This experiment was designed to compare the manner of the tumor development in female hosts. Four groups of four female rats each (165 to 185 grams) were inoculated intraperitoneally with a suspension of 100 mg. of tumor. The tumor was growing between the lobes of the liver and was obtained 31 days after transfer. It was in the tenth generation. These findings were similar to those of Experiments 1 and 2 except possibly that the tumors developed more rapidly.

Development at 7 days: The four hosts sacrificed at 7 days showed early omental tumors similar to those described in the previous experiments and illustrated by Fig. 6. Tumors were found in the other usual sites.

Development at 14 days: Four rats were sacrificed 14 days after inoculation. In one host the omental tumor (1 by 4 by 4.5 cm.) was more advanced than those found in Experiments 1 and 2 and there were numerous tumors and implants in all the usual sites. In two others the tumors were much more advanced. In one rat the omental tumor measured 1 by 4.5 by 4.5 cm. and in the other 1 by 5 by 7 cm. In

the latter the caudate lobe was embedded in a tumor measuring 1 by 2 by 2.5 cm. Other tumors were found in both hosts. The fourth rat showed only a few tumors.

Development at 21 days: In three of the four rats sacrificed at 21 days no particular findings were noted other than tumors in the usual sites which ranged in size to 1 by 1 by 2 cm. The fourth rat had extensive tumor growth and 69 ml. of ascitic fluid. The omental tumor was 1 by 4.5 by 6.5 cm. and was an advanced tumor. Numerous other tumors were found. One hundred milligrams of the omental tumor were transferred to three young male hosts. They were sacrificed at 19, 28, and 38 days because of extensive tumor growth.

Development at 28 days: Only one of the four rats survived 28 days. In this rat only small tumors were found and none in the omentum or liver site. One host died at 18 days with an omental tumor, 1 by 4 by 6 cm., and numerous tumors in all the other sites. A second rat died at 21 days and showed an omental tumor, 1 by 4 by 5.5 cm., a liver site tumor, 1 by 2.5 by 4 cm., and tumors in all the usual sites. The third rat died at 27 days and showed an omental tumor, 2 by 3.5 by 5.5 cm., a liver site tumor, 1 by 2 by 2 cm., and genital fat tumors. These three hosts had 19, 17, and 41 ml. of ascitic fluid, respectively.

Ovaries and Estrus Cycles of Tumor Hosts

In many instances at autopsy of the tumor hosts the ovaries appeared abnormal. They were small and yellow and composed chiefly of corpora lutea. It seemed of interest to make microscopic examinations of these ovaries and also those showing other abnormalities. Seventy-three ovaries from 44 tumor-bearing rats were examined. In general, the changes observed were not striking but several instances of tumorlike changes were observed. In ovaries which were essentially normal there was a tendency toward luteinization and an absence of follicles and interstitial tissue. In ovaries in which follicles were present there was a tendency toward irregular arrangement of the granulosa cells. Since the tumor resembles ovarian stroma cells, it was difficult to distinguish minor changes. In several instances tumorlike development appeared to arise from old corpora lutea. In two rats small spherical tumors arose from ovarian tissue in the region of the hilum. Although the genital fat was the site of extensive tumor formation and the ovary was often completely encapsulated by tumor, in general the tumor did not invade the ovary itself. Twenty ovaries were transferred, usually by the tissue implantation technique, but there were no successful transfers of tumor tissue.

In one host (FP 125) both ovaries were replaced by smooth bright yellow spherical masses. The right weighed 26 mg. and the left, 58.4 mg. The latter had a small corpus luteum on the surface. The tissue was firm and translucent and was similar to a young tumor. Microscopically the tissue resembled the tumor of the host but there were other cell types present also. One tumor seemed to have arisen from an old corpus luteum but in general ovarian structures were absent. Sixteen and eight-tenths milligrams of the left tumor were inoculated but failed to "take." The cycle predominated in the estrus phase.

The changes in the ovaries were less marked than those found in a series of transfers from the tumor of the ovariectomized rat FP 0456⁴ mentioned briefly above. In the second generation of this tumor all four female hosts showed marked ovarian pathology. In one host both ovaries contained abnormally large and degenerate corpora lutea and one ovary measured 3 by 3 by 5 mm. The second rat had one relatively

normal ovary but it was attached to the tumor in which it was embedded. The other ovary had been completely replaced by a solid ovarian tumor approximately 5 mm. in diameter. This tumor was pale yellow translucent tissue resembling a fibroma. Microscopically some of the tissue resembled the other tumors of the host but these areas were interspersed with fibrous tissue and tissue of other cell types. In the third rat one ovary was normal but the other had been replaced by a 10 mm. tumor. This tumor was composed of firm fibrous tissue with corpora lutea scattered throughout. On microscopic examination the corpora lutea appeared to have been invaded almost completely by tumor tissue. In the fourth rat one ovary was grossly normal but the other had a 3 by 6 mm. tumor arising from it. The ovarian tissue was old corpora lutea. Although the tumor retained some of the contours of the old corpora lutea as though they had been invaded and enlarged by the tumor no other ovarian tissue was observed.

Because of the ovarian changes, estrus cycles were followed in a group of rats beginning either prior to the transfer of the tumor or on the day of transfer and continuing to the terminal stages. When the estrus cycles were plotted graphically, ten showed a tendency toward an estrus phase, one to diestrus, and thirty to normal cycles. This incidence of a tendency toward the estrus phase may be somewhat higher than normal. The estrus smears were not similar to those obtained when cornification appears from routine vaginal smearing. Of the 41 of these rats that developed tumors, microscopic examinations were made of the ovaries of 16. There were no significant findings in the correlation of the estrus cycles with the microscopic findings in the ovaries.

Pregnancy and Tumor Development

Several attempts were made to test the effect of the tumor upon fertility and on the course of pregnancy.

Six females of known fertility were inoculated intraperitoneally with 50 mg. of tumor tissue. After 23 days they were to be mated with six males of known fertility. Two of the female hosts died from extensive tumor development at the end of three weeks and before mating. Two failed to become pregnant; one of these died from the tumor on the thirty-second day after inoculation; the other was negative after 59 days. One host did not show tumor growth at the time she delivered a small normal litter but at 102 days died with extensive tumor formation including an omental tumor, 2.5 by 4 by 5.5 cm. The sixth rat died from the tumor on the eleventh day of pregnancy and the thirty-fifth day after inoculation. Autopsy revealed seven macerated fetuses.

Five males of proved fertility received 50 mg. of a suspension tumor intraperitoneally 23 days prior to mating. One rat died on the twenty-first day, one on the twenty-third day, one on the twenty-eighth, and one on the thirty-sixth day and before adequate tests could be made. Only one of the nine females became pregnant. The fifth host survived 84 days and four of the eight females mated with this host had normal litters.

Five pregnant rats with histories of two to four normal pregnancies were inoculated intraperitoneally with 50 mg. of tumor tissue on the twelfth day of pregnancy. One died four days after inoculation; of the three that developed extensive tumors, two failed to go to term and one delivered a litter of four at term; the fifth host delivered a litter of three at term but autopsy revealed only one 1 cm. tumor in the omentum.

Another pregnant rat with a known pregnancy history was inoculated on the thirteenth day of pregnancy. A litter of six slightly undersized young was born at term. The young survived in spite of the inadequate care the mother was able to give. The mother died 32 days after inoculation and 23 days after delivery. At autopsy 92 ml. of ascitic fluid were removed from the abdominal cavity and characteristic exten-

sive tumor growth was observed. Tumors were found throughout the abdominal cavity, in the mesentery, on the diaphragm, genital fat, under the liver, and included a tumor of the omentum measuring 1 by 2 by 4 cm., a tumor under the liver measuring 2 by 2 by 3 cm., and a mesentery tumor 1 by 2 by 3 cm.

In general, these preliminary experiments show little evidence that either the course of pregnancy or the tumor growth influenced the other co-existing condition except possibly to have a deleterious effect upon pregnancy.

Summary

A transplantable rat sarcoma arising in a colony of ovariectomized rats used for the assay of estrogens has been investigated. The tumor was transmitted by transfer of tissue fragments or by inoculation of a suspension of tissue. Bacteriologic examinations were negative and the tumor was not transmitted by filtrates of tumor tissue.

The tumor was carried on in eleven lines: three lines for 10 generations, one each for 12, 17, and 19 generations, two each for 21 and 22, and one for 24. No line died out spontaneously. No tumors regressed.

The tumor remained characteristic regardless of the site of transfer and did not change type at any time. The transplantability increased with repeated transfer.

Of the 1,171 transfers made by intraperitoneal inoculation, 839 (71.7 per cent) were successful irrespective of the amount of tissue transferred. In a group of 436 hosts which received 100 mg. of tumor tissue, 353 hosts (81.0 per cent) developed tumors. Eighty and eight-tenths per cent of the male hosts (257 of the 318 hosts) showed successful transfers and 81.4 per cent of the female hosts (96 of the 118 hosts), indicating no sex difference in the susceptibility of the hosts to the tumor.

In a group of 383 hosts which received 100 mg. of tumor tissue, 318 (83 per cent) were successful. Of these, 43 hosts (13.5 per cent) survived less than 20 days, 136 hosts (35.5 per cent) survived 20 to 29 days, and 139 hosts (36.3 per cent) survived longer than 30 days.

The sites of the tumor development in a group of 179 hosts receiving 100 mg. of tumor tissue intraperitoneally and surviving less than 30 days were: omentum 176, liver and adjacent tissues 171, genital fat 156, implants 198, mesentery 149, diaphragm 91, subcutaneous 53, intestinal tract 23, kidney and adjacent tissues 14, spleen 4, thoracic cavity 3, and stomach 1. Other sites of tumor formation observed were the ovary, testis, seminal vesicle, thymus, lymph nodes, heart, and lung. Ascitic fluid accompanied advanced tumors. The greatest number of sites of tumor formation in one host was ten. Forty-seven of the 179 hosts (26.3 per cent) showed tumors in seven sites. One hundred and fifty-six hosts (87.1 per cent) had tumors in four to eight sites.

Amounts of tumor tissue from 0.5 to 100 mg. were transferred. The group of hosts receiving 40 mg. or less showed a slightly lower percentage of "takes" than those receiving 50 or 100 mg. of tissue.

The transplantability of the tumor increased with repeated transfers. Three chronological groups of male hosts composed of 31 groups of three hosts each received transfers from 92 tumors. The earliest group showed 72 per cent successful transfers, the second group 79.6 per cent and the latest group 90.3 per cent.

Three experiments were carried out to determine the mode of transmission and the rate of development of the transfers. A large group of hosts was inoculated and small groups were sacrificed at weekly intervals. Tumor development at the various intervals is described. Tumors were observed at seven days.

The effect of tumor growth on the estrus cycle and upon the ovaries has been investigated.

Several experiments were undertaken to determine the effect of the tumor upon fertility and the course of pregnancy, and of pregnancy upon the tumor development.

References

1. Curtis, M. R., Bullock, F. D., and Dunning, W. F.: *Am. J. Cancer* 15: 67, 1931.
2. McEuen, C. S.: *Am. J. Cancer* 36: 383, 1939.
3. Ratcliffe, H. L.: *Am. J. Path.* 16: 237, 1940.
4. Jenney, F. S.: *Cancer Research* 1: 406, 1941.
5. McEuen, C. S.: *Am. J. Cancer* 34: 184, 1938.
6. Watts, R. M., and Adair, F. L.: *Cancer Research* 1: 638, 1941.
7. Watts, R. M., and Adair, F. L.: *AM. J. OBST. & GYNEC.* 47: 593, 1944.
8. Dunham, L. J., Watts, R. M., and Adair, F. L.: *Arch. Path.* 32: 910, 1941.
9. Watts, R. M., and Adair, F. L.: *AM. J. OBST. & GYNEC.* 46: 183, 1943.

✓ CESAREAN SECTION MORTALITY*

WILLIAM J. DIECKMANN, M.D., CHICAGO, ILL.

(From the Department of Obstetrics and Gynecology, The University of Chicago, and the Chicago Lying-in Hospital)

THE maternal mortality from cesarean section in the United States, according to a review published in 1941, by Gordon and Rosenthal, is probably "at least 10 per cent and possibly approaches 15 per cent." Such a high mortality seems improbable, but various reports since 1930, still give mortalities for cesarean section of 0 to 17 per cent. Earlier reports give figures which are even higher for some small hospitals. Furthermore, studies of maternal deaths reveal that cesarean section had been performed in 24 per cent of the deaths in the Fifteen State Study, in 20 per cent of the New York City deaths, in 14 per cent of the Philadelphia deaths and in 20 per cent of the Chicago deaths. Five United States maternity hospitals staffed by trained obstetricians have performed 6,335 cesarean sections since 1931, with an *uncorrected* average maternal mortality of 1.46 per cent, range from 0.61 to 3.1 per cent. The reduction of the cesarean mortality in Philadelphia from 6.1 to 1.3 per cent, the report by DeNormandie of 11,030 operations in Massachusetts with a mortality of 2.46 per cent, and our own results indicate that cesarean section can be performed with a mortality of 1 to 2 per cent in general hospitals and a mortality of 0.5 to 1 per cent in maternity hospitals.

Phaneuf, in 1943, stated in a discussion that the maternal mortality from cesarean section of 1.96 per cent at the Philadelphia Lying-in

*Presented at a meeting of the Chicago Gynecological Society, Nov. 17, 1944.

Hospital was not excessive. He also stated that many of the deaths after cesarean section are attributed to the operation instead of to the existing pathology (placenta previa, abruptio placenta, contracted pelvis, toxemia, etc.). Unfortunately, a compilation Table I, of 1,922 cesarean deaths reveals that 38 per cent of the deaths were due to sepsis, 30 per cent to shock and hemorrhage and 19 per cent to toxemia, a total of 87 per cent. Certainly one-half and possibly two-thirds of these deaths are preventable.

TABLE I. AUTOPSY FINDINGS IN 1922 CESAREAN SECTIONS

CAUSE OF DEATH	RANGE %	AVERAGE %
Peritonitis, septicemia, ileus, intestinal obstruction	27 to 50	38
Pulmonary embolism	0 to 11	7
Shock and hemorrhage—total	21 to 36	30
Placenta previa	0 to 9	5
Abruptio placenta	0 to 7	6
Heart failure	0 to 9	5
Eclampsia, toxemia, vascular-renal disease, pulmonary edema	8 to 37	19
Lobar pneumonia	0 to 14	3
Anesthesia—aspiration pneumonia	0 to 12	3
Spinal anesthesia		(3)
Incompatible blood transfusion		(2)
Tuberculosis		(1)

() = Based on small number.

Plass reported that in Iowa, 29 per cent of the cesarean section deaths occurred on the first day, and 22 per cent on the second and third postoperative days. Obviously, almost 51 per cent of the deaths were from shock and hemorrhage or overwhelming infection. We are responsible for any puerperal infection, even in elective operations, until evidence is presented to the contrary. Blood transfusions will prevent death from hemorrhage.

Beck states: "The general idea that most of us hold is that the mortality from cesarean section ought not to be over 1 per cent, if the right operation is done on the right patient at the right time. We pay too much attention to indications and too little attention to contraindications."

Irving believes that when cesarean mortality in large clinics over a period of years is less than 1 per cent, then it will be time to broaden the indications. Schumann believes that cesarean section in skilled hands has a maternal mortality so low as to be practically negligible. Data in a subsequent table do not confirm Schumann's belief. There is an inevitable difference in the mortality between private and clinic patients. The clinic patient may not have seen a doctor, or there may have been errors in judgment made by the resident staff. Thus, there was only one cesarean section death (tuberculous meningitis) in our private patients who comprise 40 per cent of our service.

Kennedy, discussing cesarean section, has stated "to place a scar in the uterus and abdomen of a young woman during her first childbirth is to suspend a guillotine over her neck for the rest of her life. Where will she be during her next labor; will she fall in the hands of an accomplished surgeon, or will she die from a ruptured uterine scar?" These remarks are pertinent, but a cesarean section performed at the proper time for a proper indication will ensure a live mother and baby. I have seen death too from vaginal delivery as well as

extensive lacerations which prevented future pregnancies and/or caused dyspareunia and marital difficulties, at times ending in divorce. Subsequent vaginal plastic surgery is not always successful and is not without mortality.

DeLee always used the term "watchful expectancy" in cases of prolonged labor. Hunt, one of our former residents, transposed this term to "hopeful procrastination." We would hope that the cervix would dilate and hope that the head would engage, but what if they did not, and how long could we hope. None of us are infallible in our judgment, but nothing arouses me more than to be called as a consultant and find: 1. patient with a borderline pelvis, ruptured membranes for 48 hours or longer, repeated attempts at medical induction of labor and many rectal examinations; or 2. patient with severe pre-eclampsia at 37 weeks, repeated attempts at medical induction of labor, and many rectal examinations. In both patients *only a vaginal examination* made early could have revealed whether or not labor would begin within 12, 24, or X hours in the first case, and if medical induction had any chance of success in the second.

Mellor's statement "Watchful waiting is an essential virtue in obstetric management, but look out for criminal procrastination just around the corner," is pointed. Book knowledge of obstetrics is necessary, but only the experience gained in clinical obstetrics will enable the doctor to decide which is "watchful expectancy," which is "hopeful procrastination" and which is "criminal negligence."

TABLE II. CESAREAN MATERNAL MORTALITY—PER CENT

	CONTRACTED PELVIS			
	ROUTH		HOLLAND	
	1911		1921	
	CLASSICAL	CERVICAL	CLASSICAL	CERVICAL
	M.M. %	M.M. %	M.M. %	M.M. %
Not in labor	3.6	1.6	3.5	0.0
Early labor		1.8	6.4*	
In labor, membranes intact	2.2			
In labor, 6 to 24 hours			7.1	0.0
In labor, 24 to 72 hours		10.0	9.1	5.7
In labor, membranes ruptured	11.4			
Frequent examinations or attempts at delivery	37.9	27.0	13.6	
After induction of labor		14.0		
No vaginal examinations, all cases—2 + days of labor			5.9	1.5
Vaginal examinations, all cases—2 + days of labor			13.5	10.5
Total mortality %:	9.4	4.2	5.9	4.3

*Labor up to 6 hours.

Routh's data for the period 1891 to 1910, given in Table II demonstrate the mortality of cesarean section after prolonged rupture of the membranes, frequent examinations or attempts at delivery. The mortality in elective cesarean section was almost as low then as it is now in many hospitals. The next comprehensive report by Holland in 1921, and the Brooklyn report in 1928, show similar data, demonstrating the high mortality after prolonged labor or vaginal manipulations. It seems unbelievable that the dangers so clearly illustrated in these three studies are still not appreciated by many obstetricians.

Consultation experience and common sense dictate that you must give the doctor some positive advice besides the "don't." A cesarean section in cephalopelvic disproportion while the patient is still not infected;

in the severe pre-eclamptic patient before convulsions have occurred; or in the patient with severe eclampsia (after 8 to 12 hours medical treatment), while the patient is still a good operative risk, is far better treatment than insistence upon vaginal delivery at any cost. Deaths do occur after vaginal delivery, but many doctors attribute them to an act of God. Each patient must be individualized, and the proper type of delivery selected for her particular complication. The obstetrician should not apologize for performing an indicated cesarean section, but he should be censured if he kills mother or baby by selecting the wrong type of delivery, whether it be by vaginal or abdominal route.

Monthly meetings in some cities by a committee of competent obstetricians, at which each maternal death is discussed, have resulted in a marked decrease in the number of deaths. Philadelphia in 1931, had 601 cesarean sections (incidence of 1.8 per cent) with 38 deaths (6.1 per cent) and in 1932, 591 operations (1.8 per cent) with 36 deaths (6.0 per cent). In 1939, there were 857 cesareans (2.8 per cent) with 11 deaths (1.3 per cent), and in 1942, 1,222 operations (2.8 per cent) with 29 deaths (2.4 per cent).

Cesarean section with survival of the patient, after several unsuccessful attempts to "break up" a breech (40 hours of labor); after "failed forceps and failed version" (two different doctors tried each) and cesarean section for a hydrocephalic head that was free in the uterine cavity; is the result of chance and is not due to good judgment or operative skill. I have repeatedly been told of such cases by general surgeons who thought that their treatment had been right because the patient survived and by obstetricians who were honest enough to admit their mistake. Realization of the possibility of death from sepsis has prompted many obstetricians to an earlier use of cesarean section while the patient is still "clean." This has caused some increase in the incidence, but an absolute decrease in the maternal mortality.

Cesarean section means the abdominal delivery of the fetus. Skeel limited the term to fetuses of more than 30 weeks' gestation or weighing at least 1,500 grams. Adair included fetuses of more than 22 weeks or weighing at least 400 grams. Eastman, Stander, Irving and Cosgrove have used Skeel's criteria. Our cesarean sections were classified according to Adair's criteria up to 1943. However, the total number of fetuses weighing less than 1,500 was only 3 per cent in 419 abdominal deliveries. There is less danger from lochiometra and peritonitis if the fetus weighs less than 1,500 grams and also much less morbidity.

I have listed in Table III, the maternal mortality for cesarean section for large series of patients from 1891 up to the present time. Laparotomies for rupture of the uterus are not included. It is disappointing to note that the average mortality is still very high. However, the results achieved in the maternity hospitals, in Massachusetts, in Philadelphia, etc., demonstrate that marked improvement has occurred in evaluating the dangers of the operation.

Winter received information from 384 operators concerning 4,450 cesarean sections performed in Germany during 1928; 316 or 7.1 per cent died. Winter divided the mortality into three groups: 1. mortality due to indications for which the operation was performed, 120

TABLE III. HOSPITAL STATISTICS

HOSPITAL	YEARS	DELIVERIES 1,500 GM. +	TOTAL MATERNAL MORTALITY %	CESAREAN SECTION			
				INCIDENCE %	MORTALITY MATERNAL	— FETAL	%
Routh—Collective	1891 to 1895			83	28.00		
Routh—Collective	1906 to 1910			711	8.10		
Holland—Collective	1911 to 1920			4,197	7.20		12.0
Bannister—Coll. 5 Brit. Mat.	1928			1,763	5.80		
Winters—Coll. Germany	1928			4,450	7.10		9.0
Brooklyn, N. Y.—Collective	1921 to 1926			1,805	7.00		8.5
New Orleans—Coll. Gyn. Soc.	1921 to 1926	16,323		300	16.10		18.9
New Orleans—Coll. King	1927 to 1936	52,629		1,108	5.90		10.8
Philadelphia—Coll. Lull	1931	23,511		573	6.80		12.8
Philadelphia—Coll. Lull	1941	30,939		594	2.46		3.3
Chicago	1910 and 1911			2,500—	2.40		
Irving—Collective	1937			7,174	2.15		9.1
Arnold—Collective	1931 to 1939			15,768	4.69		8.8
Massachusetts, De Normandie	1937 to 1942				2.46		
Chicago Lying-in	1931 to 1944	272,752	0.150	11,030	3.30		
Chicago Lying-in	1942 to 1944	*39,709 ^a	0.080	1,790 ^a	4.74		8.7 ^a
Boston Lying-in	1931 to 1936	7,394 ^b	0.250	317 ^b	0.00		4.4 ^b
Boston Lying-in	1912 and 1943	*20,364	0.160	584	2.86		8.8
New York Lying-in	1932 to 1939	*9,632	0.240	925	2.34		6.5
Philadelphia Lying-in	1932 to 1942	*27,125	0.400	577	2.13		
Margaret Hague	1932 to 1943	*22,754	0.290	1,322	5.80		8.2
		*68,786		1,837	1.52		
*Total		188,370	0.244	6,335	3.36		
Rotunda—Ireland	1938 to 1940		0.430	104	4.00		6.0
Glasgow Royal Mat.	1940	6,414	1.500		1.62		
Edinburgh Royal Mat.	1938	3,032	1.500	206	6.70		
Queen Charlotte	1942	2,058	0.430	77	3.70		8.1
Women's Hosp., Melbourne	1920 to 1935	2,312		21	0.91		9.5
		43,727			0.80		

^a = Fetus weighed 400 Gm. or more.^b = Fetus weighed 1500 Gm. or more.

Coll. = Collective.

*For total.

TABLE IV. CESAREAN SECTIONS PERFORMED BY ONE OPERATOR

		NUMBER	MORTALITY %	
			MATERNAL	FETAL
Schumann	1939	120	0.00	2.5
Phaneuf	1934	575	4.20	5.9
Phaneuf—Consecutive low cervical		292	2.30	
Marshall	1939	246	0.00	5.7
Gustafson	1931 to 1943	208	0.96	3.3
Davis	1931 to 1944	450+	(3)	
Dieckmann	1931 to 1944	375+	(1)	
Hesseltine	1931 to 1944	250+	(2)	

() = Number of patients who died.

TABLE V. CESAREAN SECTION DEATHS OF CHICAGO LYING-IN HOSPITAL
(1931 TO 1944)

PATIENT	INDICATION	LIVED	TYPE OPERATION	CAUSE OF DEATH
1. As.	Tuberculous meningitis	11 days	Lap. Trach.	(A) Tuberculous meningitis
2. Gr.	Tuberculous meningitis	4 hours	Classic	Tuberculous meningitis
3. Se.	Contracted pelvis	25 hours	Classic	(A) Abdominal hemorrhage
4. An.	Myoma	9 days	Classic and Myomec- tomy	(A) Peritonitis
5. Da.	Placenta previa	3 hours	Lap. Trach.	(A) Exsanguination
6. Ge.	Cardiac disease	11 weeks	Lap. Trach.	(A) Peritonitis, acute endo- carditis
7. Cu.	Cardio-vascular-renal	17 hours	Classic	(A) Cardiac failure, anemia, chronic nephritis
8. Hi.	Placenta previa	16 days	Lap. Trach.	(A) Pulmonary embolism
9. Sz.	Disproportion, dia- betes, inertia	10 days	Cesarean- hyster- ectomy	(A) Peritonitis
10. Le.	Coma, hypertensive encephalopathy	26 hours	Lap. Trach.	Cerebral hemorrhage; eclampsia?
11. Ho.	Pre-eclampsia	29 days	Lap. Trach.	(A) Pulmonary embolism

*A live baby was delivered in each case.

(A) = Autopsy.

"Lap. Trach." = Laparotrachelotomy.

Patients 1 and 2 were delivered by cesarean section only in the interest of the baby.

Patients 3, 4, 5 and 6 died because of lack of experience of the surgeon.

Patient 7 should have had more than one blood transfusion and a longer period of bed rest before delivery.

Patient 8 spotted daily but the obstetrician in charge examined and felt placenta but did nothing for four days. The temperature rose to 39 degrees within twenty-four hours of operation and remained high.

Patient 9 might have lived had a strict peritonitis regime been maintained.

Patient 10 was in deep coma and required no anesthesia for the operation; she was considered moribund.

Patient 11 died of pulmonary embolism and was nonpreventable.

(2.7 per cent); 2. mortality due to operation itself, 185 (4.2 per cent); and 3. mortality due to intercurrent disease, 11 (0.3 per cent). He reported an operative mortality of 5.3 per cent in the University Clinics (total mortality of 8.6 per cent) which is much too high.

Data for individual operators is given in Table IV, and indicates that cesarean section can be performed by specialists with a very low mortality. The figures given for Davis, Hesseltine and myself are for operations either performed by us as surgeon or as first assistant to the resident. We have learned that one must not take chances with the life of a patient. If there are any contraindications to laparotrachelotomy, either cesarean-hysterectomy or vaginal delivery (craniotomy if necessary) is performed.

Data concerning our cesarean deaths, Table V, indicate that poor judgment or lack of skill were responsible for 7 of the 11 deaths.

I have listed in Table VI, the Brooklyn statistics, the maximum mortality rates for various obstetric complications, and the number of

TABLE VI. CESAREAN SECTION MORTALITY FOR VARIOUS COMPLICATIONS

	MORTALITY			
	BROOKLYN, N. Y. 1928		CHICAGO LYING-IN	LAPARO- TRACHEL- OTOMY
	MATERNAL %	TOTAL FETAL %	DEATHS NUMBER	MAXIMUM %
Obstructing tumors	6.0	4.8	1	1.0
Contracted pelvis, cesarean section	5.8	3.8		0.3
Cesarean section—elective				0.2
Test of labor			1	0.4
Repeat	0.8	7.0	1	0.3
Placenta previa	7.0	19.0	2	2.0
Large fetus and postmaturity	5.4	8.1		0.4
Elderly primipara	15.0			0.4
Eclampsia	27.0	26.0	1	13.0
Nonconvulsive toxemia	7.0	15.0	1	2.0
Abruptio placentae	0.0	63.0	0	5.0
Malposition				0.4
Heart disease	4.8	4.7	2	3.0
Fetal indication				0.2
Previous pelvic operations	4.0	12.0		0.2
Cervical dystocia	4.5	2.0		0.4
Abnormal uterine rings	29.0	29.0		1.0
Total number deaths:	126		9	
Total number operations:	1,759		1,788	

our own deaths. These figures are based on collective studies. One must remember that there is a mortality associated with some of these complications irrespective of the type of delivery. The maximum total mortality rate for cesarean section should be 0.5 to 1.0 per cent, but in the treatment of contracted pelvis, elective cesarean section should have a maximum maternal mortality of 0.2 per cent and after a test of labor, 0.4 per cent.

Indications for Laparotrachelotomy

Elective Indications

1. *Tumors* (uterine or ovarian) blocking the pelvis should have been diagnosed before labor or early in labor.

2. *Contracted Pelvis—Cephalopelvic Disproportion.*—Our practice is to perform an elective cesarean if the true conjugate is less than 8.0 cm., or the transverse diameter of the outlet is less than 7 cm. with the baby estimated to weigh 3,000 grams or more. With the true conjugate greater than 8.0 cm., the patient is given a test of labor. This means that the patient has hard uterine contractions at 3 to 5-minute intervals, lasting at least 35 seconds, for 12 to 18 hours. A maximum of two rectal and two vaginal examinations are made. These patients should have at least one vaginal examination after some hours of labor before they are subjected to the risk of cesarean section. If in this length of time the cervix has not dilated satisfactorily, or the head has not descended to the level of the spines, cesarean section is performed. We do not expect delivery in 24 hours. *Our deadline is 24 hours of ruptured membranes or labor.* In patients who are in labor for a longer period, delivery is effected vaginally, if necessary by craniotomy, or by cesarean-hysterectomy. All statistics show that the bacterial content of the uterus increases progressively after 12 hours of ruptured membranes or of labor, and that if a cesarean section is performed, the morbidity parallels the duration of labor or ruptured membranes. The ideal test

of labor is strong uterine contractions for 1 to 2 hours with complete dilatation of the cervix and ruptured membranes, providing it occurs within the first 24 hours of labor. Unfortunately, many of our patients never reach the second stage even after 36 to 48 hours of labor.

3. *Repeat Cesarean Section.*—Rupture of the uterus has a hospital incidence of 0.05 per cent. Recent reports from maternity hospitals give an average maternal mortality of 40 per cent, range 20 to 80 per cent, and an average fetal mortality of 65 per cent. Various studies of maternal mortality reveal that 6 to 15 per cent of the deaths are due to uterine rupture. Twenty to 100 per cent of the spontaneous ruptures, especially where there was no dystocia, are due to rupture of a uterine scar. Holland reported that after classical cesarean section by experienced obstetricians, the incidence of rupture was 4 per cent, but if labor had commenced the incidence was 19 per cent. The incidence of rupture of the cervical scar is at least 0.3 per cent. These³ statistics are difficult to obtain. Reports of rupture of the scar rarely give the number of cesarean sections performed, the number who became pregnant again, and, especially those who were delivered vaginally. During the past 13 years, 1,790 cesarean sections were performed by us and only one uterus with a cesarean scar ruptured with escape of the fetus into the abdominal cavity. This patient had been permitted to go into labor and while preparations were being made for operation, the uterus ruptured. In at least six more patients, when the bladder had been separated for a repeat cesarean section, there was found a complete separation of the scar. These patients were not in labor, and there had been no symptoms or signs of the separation, but had labor begun, the fetus would undoubtedly have been extruded into the abdominal cavity. A survey of the literature as well as personal experience indicate that the lower uterine segment scar is less likely to rupture than the classical.

It was thought for many years that uterine incisions heal by regeneration of muscle tissue. Schwarz and his associates have demonstrated both in the experimental animal and in the human that healing takes place by the usual fibrin seal and subsequent proliferation of fibroblasts. There is no way by which the strength of the scar can be detected. Patients have had two vaginal deliveries after cesarean section, and then a uterine rupture with the fourth labor. If the placenta is over the scar, it seems that the incidence of rupture is increased. Therefore, if vaginal delivery is contemplated, an attempt should be made to determine the location of the placenta by x-ray visualization. I can find no evidence that the transverse incision of the lower segment is less likely to rupture. In view of the high maternal and fetal mortality due to uterine rupture and the impossibility of knowing which scars will not rupture, a previous cesarean section in general warrants a repeat operation. It should be performed 7 to 14 days before term. Tubal ligation (hysterectomy in patients past 35) should be advised at the second operation and insisted upon at the third. Catholic patients are best treated by cesarean-hysterectomy after the second or third operation. Physicians have reported six, seven, and even nine cesarean sections on the same patient. In many of these cases the uterus was reported as being adherent to the abdominal wall, which probably accounts for the survival of the patient. Most statistics indicate that the

elective repeat cesarean section has a lower mortality than that of the primary operation. However, cesarean mortality is higher than that after normal vaginal delivery. Therefore, the patient should not be subjected to an unlimited number of cesarean sections.

Some obstetricians do not believe "once a section, always a section," but if they guess wrong, the baby is lost and the mother is subjected to a mortality of 40 per cent, while an elective cesarean section would have subjected her to a mortality of less than 0.5 per cent, and a fetal mortality of less than 2 per cent. We have permitted vaginal delivery only: 1. if the patient entered the hospital in active labor with five or more centimeters' dilatation and no disproportion, 2. if the pregnancy was less than 36 weeks' gestation, or 3. if the baby was dead and then delivery was by craniotomy as soon as there was 8 cm. dilatation.

TABLE VII. PLACENTA PREVIA MORTALITY

HOSPITAL	TOTAL CASES			VAGINAL DELIVERY			CESAREAN SECTION		
	MORT. %			MORT. %			MORT. %		
	NO.	MAT.	FET.	NO.	MAT.	FET.	NO.	MAT.	FET.
Chicago Lying-in	258	0.77	32.0	152	0.00		106	1.88	
Boston Lying-in	548								
Margaret Hague	341	0.58		237	0.88		104	0.00	
Cleveland Maternity	160	0.80	25.0	38	0.00		122	1.65	
Philadelphia Lying-in and Jefferson Maternity	166	6.60			4.90			8.30	
Sloane's and Women's	400	5.30		274	4.70	38.0	126	6.30	11.0
Total:	1,829	2.84		796	2.89		614	2.44	
British-Berkeley	4,580	7.00		818	5.50	68.0	414	4.10	23.4
Collective—Bill				2,117	9.70		262	1.78	
Collective—Mackenzie					8.00	54.0		6.60	17.0
Collective—Kellogg					5.10	63.0		4.00	
Collective—Davis					7.70	57.0		6.50	15.0
Collective—Findley					6.00	57.0		6.00	24.0

4. *Placenta Previa*.—The extensive study by Berkeley of 4,580 cases from leading British maternity hospitals and collective reviews by McKenzie, Findley, Davis, Irving and Bill, as well as the results from several American maternities are given in Table VII. These data show that vaginal delivery is accompanied by a maternal mortality ranging from 0 to 11 per cent with an average of 6 for all hospitals and 3 per cent for maternity hospitals. Delivery by cesarean section has a range of 0 to 11 per cent with an average of 4 per cent for all hospitals and 2.4 per cent for maternity hospitals. The cause of death in placenta previa is either from hemorrhage or from infection. If vaginal delivery is carried out, only the most expert care will prevent tears in the fragile lower uterine segment. Kellogg and Irving state that the inexperienced physicians have a lower maternal mortality with cesarean section than with vaginal delivery. I qualify this by adding if rupture of the membranes does not control the bleeding. If the insertion of a bag or Braxton Hicks version are required to control the hemorrhage, Watson's studies showed that 69 per cent of the cases required a serious operative delivery. It is disappointing to note that only 5 to 20 per cent of the patients received blood transfusions, and many authors and reviewers commented that the patients were not given enough blood, especially after delivery. Death from hemorrhage is again the old story of too

little and too late. Our practice is to classify the case as a *complete* placenta previa if the internal os at the time of the examination, irrespective of the amount of dilatation, is completely covered with placental tissue, and *incomplete* if the os is only partially covered. Any patient who is 30 weeks or more pregnant with complete placenta previa is best treated by cesarean section. Approximately 25 per cent of the patients fall in this class. It is difficult to lay down any hard and fast rules, but in general, cesarean section is the operation of choice in the treatment of placenta previa. Where the placenta is palpated one or more centimeters from the os, or where it cannot be palpated but is said to be low lying, vaginal delivery can usually be safely carried out. Early and repeated transfusions will aid in decreasing maternal mortality.

Diagnosis of Placenta Previa Is by Vaginal Examination.—Visualization of the placenta by x-ray is not perfect or always feasible, nor does it give information as to the degree of previa.

Irving, Greenhill and Davis believe that the incidence of fetal monstrosities is increased in patients with placenta previa. Murphy could find no significant increase. This possibility should not deter one from performing cesarean section. The mother's life is of paramount importance.

DeLee repeatedly stated that the lower segment operation was especially indicated in cases of placenta previa because one could suture bleeding maternal sinuses. If the placenta is on the anterior wall, bleeding from the low cervical incision is controlled only with great difficulty. Therefore, many obstetricians perform the low classic incision because there is less operative hemorrhage.

The gynecologist has known for many years that the incidence of peritonitis after myomectomy if the uterine cavity is opened is markedly increased in those patients who have had persistent uterine bleeding for days. This increased susceptibility to infection is due chiefly to the increased bacterial count (possibly increased virulency) caused by the constant presence of blood in the vagina. Thus, the patient who has been bleeding from placenta previa for days is quite likely to develop a puerperal infection after cesarean section even if no examinations are made. Vaginal instillations should be used. Hysterectomy may be necessary.

5. *Breech presentations* in patients with contracted pelvis or in elderly primipara with large babies warrant elective cesarean section.

6. *Transverse presentations* in primipara and recurrent transverse presentations in multipara are frequently best treated by elective laparotrachelotomy.

7. *Heart Disease.*—Patients who have fully recovered from cardiac decompensation during pregnancy are occasionally delivered by cesarean section at a time thought most opportune.

8. *Previous Operations.*—Extensive vaginal or cervical plastic operations and previous radium application to the cervix frequently necessitate laparotrachelotomy.

9. *Fetal.*—Elective cesarean section is justified in the interest of the baby in some patients, although it increases the risk for the mother

(elderly primipara, previous sterility, low fertility, previous repeated stillbirths, fetal asphyxia in early labor). This is especially true if there are several major complications present.

Relative Indications

1. *Large Fetus—Postmaturity.*—The incidence of postmaturity is approximately 7 per cent and of fetuses weighing over 4,500 grams is 1 per cent. There is a definite correlation between postmaturity (294+ days) and fetuses weighing over 4,000 grams. The length of labor, incidence of cesarean section and fetal and maternal mortality are definitely increased. Postmaturity, if the menstrual history is correct, should cause no concern, providing there is no disproportion or other complications. A large fetus, as determined by abdominal palpation or measurement (McDonald or Ahlfeld method), is always of concern. No attempts at inducing labor should be instituted. When spontaneous labor begins, it must be conducted as a "test of labor." Stereoscopic anteroposterior and lateral x-ray films during labor may be of diagnostic value.

2. *Elderly Primipara.*—Consensus of opinion defines elderly primipara as patients who have their first child when they are 35 years of age or over. Kuder and Johnson report an incidence at the New York Hospital of 2.7 per cent. They noted an increase incidence of toxemia, contracted pelvis (especially funnel), prolonged labor, myoma and an increased maternal and fetal mortality. Our practice in these patients near term is, if possible, to permit our usual test of labor. If the membranes rupture prematurely, and if labor cannot be started with fractional doses of pituitrin, and if the pelvis is empty, we will perform a cesarean section within 24 hours.

3. *Toxemia of Pregnancy.*—The mortality from cesarean section in the treatment of eclampsia ranges from 2 to 88 per cent. This is readily understandable when one realizes that the mortality in the United States for cesarean section is approximately 5 per cent, and for eclampsia is 13 per cent. It is obvious that the expert obstetrician will have a very low mortality from cesarean section, even when the patient has eclampsia, if the latter has first been treated medically. The indiscriminate use of cesarean section in the treatment of eclampsia or operations by inexperienced surgeons results in mortality rates that are appalling. Cesarean section is indicated in toxemic patients if there is cephalopelvic disproportion. In pre-eclampsia where the blood pressure, proteinuria and edema are increasing despite treatment, or where symptoms develop and the cervix is not effaced, an elective cesarean section is indicated. Only the patient with the *severe type of eclampsia and an uneffaced cervix should after 8 to 12 hours of proper medical treatment be delivered by cesarean section.* The patient is certainly a better risk for operation at this time, than if one waits until she is moribund and then attempts to save her by cesarean section. Patients with mild eclampsia are treated medically for days until the cervix is effaced. Approximately 40 per cent of the patients have antepartum eclampsia, but only one-fourth of the cases is severe. During the past thirteen years, we have treated 86 patients with eclampsia and cesarean section has been performed in only 12 (14 per cent). In some of these, the operation was performed on account of disproportion, or the convulsions occurred after the delivery.

Approximately 11 per cent of our patients with pre-eclampsia and 21 per cent with vascular-renal diseases are delivered by cesarean section. It is the method of choice in patients with severe vascular or renal disease if the pregnancy has to be terminated between 32 and 38 weeks in the interest especially of the fetus. Tubal ligation (sterilization) per se is not an indication for cesarean section.

In the period under report, there were 241 (7.0 per cent) cesarean sections in 3,102 patients with nonconvulsive toxemia. In many of these patients, there have been several indications for cesarean section, none alone being sufficient, but the combined indications warranted the operation.

TABLE VIII. ABRUPTIO PLACENTAE MORTALITY

HOSPITAL	TOTAL CASES			VAGINAL DELIVERY			CESAREAN SECTION		
	MORT. %			MORT. %			MORT. %		
	NO.	MAT.	FET.	NO.	MAT.	FET.	NO.	MAT.	FET.
Chicago Lying-in	225	1.33		156	1.92		69	0.0	
Margaret Hague	414	0.48		342	0.58		72	0.0	
Boston Lying-in	353	11.30		252	11.50		99	11.0	
New York Lying-in	93	3.20							
Total:	1,085	4.40		750	4.50		240	4.6	
Collective—Bland	2,319	6.30	66.0	414	4.10	61.0	107	11.2	74.0
Collective—Irving		5 to 10	60 to 90						
Collective—Weymeersch			63.0		6.60	61.0		21.0	70.0

4. *Abruptio Placentae*.—Collective reviews by Bland and Rakoff, and Irving reveal that the maternal mortality ranges from 0 to 18 per cent with an average of 6.3, and the fetal mortality ranges from 55 to 100 per cent with an average of 66 per cent. The average maternal mortality for vaginal delivery was 4.1 per cent and for cesarean section was 11.2 per cent. The data in Table VIII, from four maternity hospitals gives an average maternal mortality of 4.4 per cent. The maternal mortality for patients treated by cesarean section was 4.6 per cent and by vaginal delivery 4.5 per cent. The consensus of opinion, with the exception of Irving, is that patients presenting evidence of deep shock, low hemoglobin, rapid pulse, a uterus larger than the period of gestation; and one in which dilatation of the cervix does not occur after the membranes have been ruptured for 6 to 12 hours, are best treated by cesarean section. During the period of observation large amounts of blood, as well as 2,000 to 4,000 c.c. of parenteral glucose and saline solutions must be given. Irving states that he has seen no postpartum hemorrhage from the so-called Couvelaire uterus. Various authors have reported on the continued bleeding from the uterus after delivery; and DeLee, in 1901, made note of the hemophiliac-like nature of some of these cases and stated that the blood failed to clot in two. Davis and McGee reported that in 10 of the 12 fatalities in their series, death was due to continued bleeding from the uterus, which could not be controlled by an intrauterine pack or by clamping the uterine arteries in two cases. We have had to remove two uteri, 2 and 6 hours, respectively, after delivery because of persistent hemorrhage. We have shown that the blood fibrin may be absent or may be reduced to such a low concentration that proper coagulation cannot occur. If the obstetrician is in doubt about possible postpartum hemorrhage, hysterectomy is advised.

Borderline Indications

1. *Breech Presentations*.—Borderline pelvis, large babies and/or faulty labor may require laparotrachelotomy after a test of labor.

2. *Malposition*.—Face and brow presentations in which dilatation is slow or fails to occur, or the head fails to engage, should be treated as cases for tests of labor and delivery if necessary effected by cesarean section.

Cesarean section followed by oophorectomy, hysterectomy or tubal ligation is a proper procedure. Myomectomy, if the tumors are in the line of incision, is indicated. Other myomas should be left alone until after the patient has her family. Hysterectomy is indicated if the tumors are numerous, or if any are 10 cm. or more in diameter. Cesarean section followed by appendectomy, cholecystectomy, etc., is indefensible and will result in increased maternal mortality.

Fetal Mortality.—The purpose of obstetrics is to ensure a live undamaged mother and baby. Cesarean section does not always accomplish this. The stillbirth and neonatal mortality are definitely increased after 24 hours of labor or ruptured membranes. Many babies survive after prolonged labor, but the incidence of brain injury is increased as a result of intracranial hemorrhage or intrauterine asphyxia. A normal fetal heart rate after prolonged labor will not always ensure a living, undamaged baby. Craniotomy, even on the living but potentially damaged fetus, is a better procedure than cesarean section after prolonged labor which not infrequently terminates in both maternal and fetal death.

Types of Cesarean Section

The increased possibility of puerperal infection after cesarean section as compared with vaginal delivery has been known for decades. I have listed in Table IX, the various types of cesarean section together with some recent mortality figures for each type of operation. Each modification has been designed to lower the maternal mortality.

TABLE IX. MORTALITY FOR VARIOUS TYPES OF CESAREAN SECTION

HOSPITAL	CLASSICAL		LOW CERVICAL		EXTRAPERITONEAL		CESAREAN-HYSTERECTOMY	
	NO.	M.M. %	NO.	M.M. %	NO.	M.M. %	NO.	M.M. %
					250 Waters	0.80		
Margaret Hague	117	6.8	1,261	1.03	181 Latzko	1.65	27	7.40
Boston Lying-in	372	2.1	168	4.20	23	0.00	21	14.30
Women's, N. Y.	235	4.3	620	2.10	34	2.94	17	5.90
Chicago Lying-in	22	18.1	1,618	0.38	1	0.00	96	1.04
Total:	746	4.0	3,667	1.07	489	1.23	161	4.30
Collective, Irving	3,334	6.7	2,006	1.85	391	4.00	212	10.40

Bacteria from the vagina gain access to the uterus during prolonged labor and during the postpartum period. Certainly by the end of the second postpartum day, all uteri contain bacteria which have usually come from the vagina. The natural resistance of the woman is her only protection against these bacteria: and she is especially resistant against those from her own vagina unless these bacteria are given special opportunities to invade, such as would occur in prolonged

labor, excessive manipulation, excessive blood loss or the retention of a piece of placenta. The postpartum uterus containing a large wound (placental site) blood clot, bacteria, and having a poor blood supply is an excellent culture tube. The experience has been that patients dying from infection after classical cesarean section usually have some separation of the uterine incision with drainage of the lochia into the abdominal cavity. Quite obviously, cesarean-hysterectomy in potentially or actually infected patients offers the best chance for their recovery. As seen from the table, the maternal mortality after cesarean-hysterectomy ranges from 1 to 14 per cent with an average of 4.3 per cent. There is no question but what the mortality would have been much higher had these uteri not been removed. The institution of a "peritonitis routine" immediately after operation and its maintenance for two or more days, or its institution as soon as the patient shows fever, tachycardia, vomiting or distention, would have undoubtedly reduced the mortality in some of the cesarean-hysterectomies.

Careful details as to vaginal preparation and the prevention of spill (in other words, much the same management that one would use in a total hysterectomy for carcinoma of the corpus) will lessen the likelihood of serious postoperative infection. One hesitates to perform cesarean-hysterectomy with the first baby. Here, the operation of choice might be craniotomy. However, a live patient without a uterus is a better result than a dead patient with a uterus.

The extraperitoneal, low cervical cesarean and other modifications have been designed to prevent the possible drainage of uterine contents into the abdominal cavity. The extraperitoneal was the first modification suggested and is theoretically ideal. Baldwin's results in the treatment of puerperal infection by hysterectomy prove conclusively that extraperitoneal section is not as safe as cesarean-hysterectomy. The data in the table indicate that the average maternal mortality for extraperitoneal section is 2.5 per cent, ranging from 0.8 to 4 per cent. Unfortunately, the majority of these patients were not infected or even potentially infected. For example, Waters states that most of their extraperitoneal sections are done for teaching purposes. This operation is dependent for its safety upon an uninjured parietal peritoneum. Any perforation, even if ligated, destroys the safety of the operation. I believe a careful study by any one of the published statistics, Table IX, as well as discussions with some of the advocates, will clearly show that this operation is not the proper treatment for the infected case.

The low cervical incision was developed to increase the safety of cesarean section by placing the uterine incision beneath the bladder peritoneum. Statements were made that since the incision was in the quiescent portion of the uterus, better healing would result. The incision can be sutured more easily than the classical incision. The safety of the operation, however, depends upon the fact that the incision is covered with a peritoneal flap which, if it has been properly sutured, will become adherent within hours and thus prevent leakage of lochia into the abdominal cavity should it occur through the uterine incision.

Marsupialization of the uterus and exteriorization of the uterus have no place in modern obstetrics.

The low cervical incision as a routine type for cesarean section results in less morbidity and less mortality than any other type of cesarean section and should be practiced by anyone performing abdominal delivery after the thirty-fourth week of pregnancy with the possible exception of cases of placenta previa or where time is a factor. In these two latter conditions, if the case is not potentially infected, classical cesarean section with proper peritonization of the uterine incision (Schumann's modification) offers the best results.

Morbidity and Puerperal Infection

The usually accepted standard of morbidity is temperature elevation. Unfortunately, other complications such as tachycardia, shock, hemorrhage, early death (before fever can develop), ileus, anemia, vomiting, etc., are not included. Many institutions take the temperature only twice daily. Their morbidity will be less than where the temperature is taken more frequently. The morbidity after cesarean section ranges from 20 to 60 per cent. The total obstetric morbidity for three maternity hospitals has been approximately 10 per cent. The incidence at our hospital for one year, of temperature elevations up to 38.9 degrees, was 5.5, and over 39 degrees, was 3.4 per cent; a total morbidity of 8.9 per cent. The incidence of serious puerperal infection was 0.4 per cent. The morbidity in the first 500 cesarean sections at our hospital was 47 per cent, in the second 500 it was 41 per cent, and in the third 500 it was 31 per cent, an average of 40 per cent for the whole group. This morbidity after laparotrachelotomy is rarely associated with sick patients such as were encountered after classical section. Vomiting and distention occurred in less than 5 per cent of our cesarean patients. We attribute this to: A. the prevention of spill (meconium, blood and amniotic fluid) into the abdominal cavity, B. limited vaginal (2) or rectal (2) examinations in patients who may be subjected to operation, and C. the use of local anesthesia.

Vaginal instillations of a 2 per cent aqueous solution of mereurochrome were started by Mayes in 1924. He reports that in the Methodist Hospital in Brooklyn with instillations they had only two deaths from puerperal infection during the delivery of 24,392 patients as compared with 25 deaths from infection during 10,368 deliveries without instillations. I instituted vaginal instillation of mereurochrome in glycerin on the Washington University obstetric service in 1926. In 1931, a change was made to 1 per cent acriflavine in glycerin. T. K. Brown reports that on this service 8 c.c. of the solution are instilled with an aseptic syringe every four hours during labor and before each rectal or vaginal examination. Patients who may be delivered by cesarean section are instilled once daily. Patients with ruptured membranes but not in labor are instilled twice daily. He states that there were 13 maternal deaths from sepsis between 1924 to 1932 (9,539 deliveries) and no deaths from infection without the use of chemotherapy from 1932 to 1941 (14,789 deliveries).

Harris and Brown obtained uterine cultures from 50 patients at section. Anaerobic growth was obtained in 45 per cent of the positive

cultures. "No sterile cultures were obtained from patients in whom active labor had lasted for six hours or more."

T. K. Brown reported that in a series of 144 cesarean sections studied at the St. Louis Maternity Hospital, the incidence of positive uterine culture was only 4.1 per cent when vaginal instillations of acriflavine were employed; and that since 1931, puerperal infection as the cause of mortality associated with cesarean section has been eliminated, apparently due to the use of antiseptic vaginal instillations.

Various investigators have confirmed the report first published by Schottmüller in 1910, and reiterated by Schwarz and Dieckmann in 1926, that over two-thirds of the cases of puerperal infection on clean obstetric services are due to anaerobic streptococci. These infections are autogenous, resulting from prolonged labor, prolonged rupture of membranes, excessive trauma at delivery, retention of a piece of placenta, lack of uterine tone. No drug to date has been found to be effective in the cure of anaerobic streptococcal infection. *Prevention is easier than cure.*

Since 1931, at the Chicago Lying-in Hospital, we have been using one per cent acriflavine in glycerin with each vaginal examination. On April 1, 1943, we substituted 1 to 1,000 merthiolate in glycerin and in addition, began making vaginal instillations of 8 c.c. every 8 hours after 12 hours of labor or ruptured membranes. Elective cesarean sections are instilled the night before, morning of operation and when the uterine packing is removed.

Vaginal instillations of an antiseptic solution are not comparable to the douches, etc., used 40 years ago. The studies to date demonstrate the value of these treatments. Until someone has shown conclusively that vaginal instillations are of no value, they should be used in patients who may be delivered by cesarean section (trial labor), in cases of prolonged labor, and in patients with premature rupture of membranes.

Reproductive History After Cesarean Section

Bride, in 1921, followed-up 190 patients who had had a cesarean section; 94 had 106 pregnancies (17 of which aborted); 66 used no contraceptives, and he concluded that there was a relative sterility of 41 per cent.

Schmelzer, in 1940, studied the fertility in 90 patients who had had a cesarean section; 83 patients had 158 pregnancies, 26 terminated by abortion, 45 by repeat section, and 87 by vaginal delivery. He concluded that cesarean section did lower the fertility slightly, especially if the first pregnancy was terminated by section.

We have not made a statistical study of subsequent pregnancies, but doubt if a relative sterility does result from cesarean section. Almost one-third of our cesarean sections was performed because of previous cesarean section. If there has been no serious endometritis, subsequent fertility is normal.

Anesthesia

Some type of anesthesia is necessary for cesarean section even though it adds to the risk. However, the obstetrician should limit himself to the use of one or two anesthetics and leave experimentation with new

anesthetics to the large clinics. Eleven, 4 per cent, of the cesarean deaths in Massachusetts over a five-year period were due to anesthesia.

Local anesthesia using one-half per cent novocain is the safest anesthetic. Sixty per cent of our operations are performed with it, and an additional 15 per cent are combined local anesthesia and inhalation. To date, we have had no maternal or fetal deaths, or complications which could be attributed to the local anesthesia. Even if a general anesthetic is to be used our chief anesthetist, Dr. P. Ouda, has demonstrated that the duration and depth of the anesthesia can be decreased if local infiltration is carried out prior to the general anesthetic. Many obstetricians use local anesthesia supplementing with gas anesthesia during the delivery of the fetus. Morphine 0.01 to 0.016 Gm. will have an immediate effect, if given intravenously as the baby is delivered.

Synephas in 1939, commented on anesthetics for cesarean section as follows: 42 deaths and 6 serious accidents occurred with evipal; there were no deaths in over 4,000,000 anesthetics for delivery using nitrous oxide, ethylene or cyclopropane; spinal anesthesia is excellent except the dangers increase as term is approached; local anesthesia is innocuous and excellent, but it may not suffice if the patient is in active labor.

Inhalation.—Since 1931, there have been over 46,000 obstetric anesthetics given at our hospital by trained physicians with some 45 aspirations during anesthesia with ethylene or cyclopropane and ether with two maternal deaths, both patients dying within 24 hours. Eight more patients were seriously ill but recovered. There have been no cesarean deaths from anesthesia, but there have been some serious cases of bronchopneumonia. Drop ether is the safest of the inhalation anesthetics. Chloroform is used by very few obstetricians, but if properly given is ideal for the delivery. It should not be used for repairs or for prolonged operative deliveries. Ethylene or nitrous oxide and ether are next in safety. There is some evidence indicating that cyclopropane is more hazardous for baby and mother, in the latter predisposing to shock, and in the former to anoxemia.

Only a liquid diet is permitted during labor and nothing is given by mouth within 6 hours of a general anesthetic. If patients have recently eaten, the stomach contents are aspirated by tube.

Intravenous.—Evipal and other intravenous anesthetics entail a definite risk because of the pregnancy (labile blood pressure, marked and sudden changes in intra-abdominal and intrapulmonary pressures).

Rectal.—Avertin as a preliminary anesthetic has an increased hazard in pregnancy as mentioned in the preceding paragraph. Ether in oil is a safe supplemental anesthetic, if there is no one capable of administering an inhalation anesthetic.

Spinal.—A number of obstetricians advocate spinal anesthesia for cesarean section. At the Margaret Hague Maternity the only contra-indication is arteriosclerosis. Cosgrove and Waters use it for patients in shock. Watter also advocates spinal anesthesia in patients who are in shock. However, most anesthetists who use spinal anesthesia warn of its dangers in patients with abnormally low or high blood pressure, or seriously sick patients. In these, they advise the use of local anesthesia.

The fatalities from spinal anesthesia in pregnancy are due to the lability of the blood pressure which reaches a maximum at term. One can collect several thousand cesarean sections performed under spinal anesthesia without any maternal mortality. However, Franken has collected 2,000 cesarean sections under spinal anesthesia with 14 deaths. If the blood pressure decreases to the shock level and persists for five minutes or longer, it may cause cerebral injury in the fetus as a result of the anoxemia. We have had one baby with cerebral injury due to prolonged shock (the mother had received no anesthesia), and one similar case has been reported after continuous caudal anesthesia, as well as one fetal death.

Marshall, Ginglinger, Brindeau, Synephas and numerous other obstetricians, although using spinal anesthesia themselves, warn of the increased risk, especially during pregnancy.

Caudal anesthesia by either a single or continuous injection entails the same dangers for mother and fetus as does spinal. Hingson has recently reiterated the dangers and contraindications for caudal anesthesia.

Our belief is that if the obstetrician has no one capable of administering an inhalation anesthetic and he is not able to perform the operation under local anesthesia, spinal anesthesia, using 80 to 100 mg. of novocain and preceded by one injection of 0.048 Gm. ephedrine, should be used. Oxygen administration may be necessary for both spinal and caudal anesthesia until the fetus is delivered.

Special Points in Technique

Spill of amniotic fluid, blood and especially meconium should be prevented by use of suction and packs. The latter cannot be properly used with local anesthesia. Spill into the abdomen is retarded by the first assistant maintaining constant tension on the traction suture, placed at the upper end of the uterine incision, or the uterus may be sutured to the abdominal wall. In patients who are not in labor, the uterine incision must be extended in most instances into the contractile portion of the uterus for 2 to 4 centimeters. If the visceral peritoneum is reflected by an elliptical incision (as used for advancement of the bladder) in place of a transverse incision, and only one flap is raised, beginning as high on the uterus as feasible, the uterine incision can be covered by this peritoneum using a tight running suture of zero chromic catgut. Additional safety is assured by a second suture line (Lembert). Thus, within 24 hours the uterine incision is sealed off from the abdominal cavity. Patients who have fever, distention, tachycardia, vomiting or excessive spill should be placed on a "peritonitis routine" (nothing by mouth, and at least 1,000 c.c. saline and 2,000 c.c. of 5 or 10 per cent glucose solution parenterally every 24 hours) for 48 hours or longer depending on the postoperative course.

The uterine incision is closed in two layers, using interrupted sutures of zero chromic for the first layer and continuous for the second. The sutures should be 1 cm. apart and not tied too tightly. The fundus of the uterus is *always* firmly packed with gauze, with only a strip of the gauze in the lower segment and vagina. This pack is inserted not to prevent hemorrhage, but to ensure a maintenance of uterine tone which

will favor the formation of the fibrin seal in the incision and promote the drainage of the lochia. The gauze is removed in 8 hours.

Daily and Dieckmann reported that the average blood loss at cesarean section by competent surgeons is 539 c.c. (range 100 to 1,410). This amount of blood with vaginal delivery is usually regarded as a post-partum hemorrhage. It was less if patients were in labor, or if 0.5 c.c. of solution of posterior pituitary was injected into the uterus after delivery of the head and after 30 seconds the fetus extracted very slowly.

Five cesarean deaths in Massachusetts in 1941, were due to transfusion accidents. These are preventable deaths. During the past year, two of our patients received incompatible blood but did not die. The fault was the lack of experience by our residents, and while we have instituted all precautions possible, we are also giving one-third less blood transfusions than we did two years ago. Naturally, if there has been extensive hemorrhage, enough blood is given in as short a period as possible to maintain a hemoglobin concentration of at least 10 grams. If time is available 4.0 Gm. NaHCO_3 are given every two hours, for 8 doses, beginning at least 12 hours before the transfusion. If there is any suspicion of an incompatible blood, 300 c.c. of molar sodium lactate are mixed with 2,700 c.c. 5 per cent glucose; 1,500 c.c. are given intravenously and the remainder by clisis.

Summary

Laparotrachelotomy in patients with cephalopelvic disproportion can be performed with a maximum maternal mortality of 0.2 per cent as an elective operation and 0.4 per cent after a test of labor (with our criteria). Other indications are usually accompanied by an increased maternal mortality, but the increase should be due to the complication and not to the operation.

Total cesarean section mortality can be kept below 1 per cent by the following evaluation of the case:

1. Is there a proper indication—elective, relative, or borderline?
2. Are there any of the following contraindications present? (a) Ruptured membranes over twenty-four hours. (b) Labor over twenty-four hours. (c) Repeated rectal or vaginal examinations. (d) Operative manipulation either for induction of labor or for delivery. (e) Uterine infection. (f) A dead or damaged fetus.
3. Will another procedure, usually a craniotomy, assure a lower maternal mortality?

Key References

Cesarean Section Statistics

- Skeel, A., and Jordan, F.: *AM. J. OBST. & GYNEC.* 23: 172, 1932.
 Routh, A.: *J. Obst. & Gynaec. Brit. Emp.* 19: 235, 1911.
 Fifteen State Study. U. S. Dept. of Labor. Publication No. 221, 1933.
 Aldridge, A., and Parks, T.: *AM. J. OBST. & GYNEC.* 36: 859, 1938.
 Marshall, C., *Cesarean Section.* J. Wright & Sons, Ltd., Bristol, 1939.
 Waters, E., *Personal communication.*
 Lull, C.: *AM. J. OBST. & GYNEC.* 46: 314, 1943.
 Schumann, E.: *AM. J. OBST. & GYNEC.* 37: 212, 1939.
 Gordon, C., and Roenthal, A.: *Am. J. Surg.* 51: 525, 1941.
 Mohler, R.: *AM. J. OBST. & GYNEC.* 45: 466, 1943.
 Gordon, C.: *AM. J. OBST. & GYNEC.* 16: 307, 1928.
 Winter, G.: *Zentralbl. f. Gynäk.* 53: 1874, 1929.
 Ricci, J., and Marr, J.: *Principles of Extraperitoneal Cesarean Section*, Philadelphia, 1942, Blakiston Co.

- Phaneuf, L. E.: AM. J. OBST. & GYNEC. 45: 476, 1943.
 DeNormandie, R.: New England J. Med. 227: 533, 1942.
 Stander, H.: Williams Obstetrics, ed. 8, New York, 1941, D. Appleton-Century Co.
 Bannister, J.: Brit. M. J. 2: 1143, 1935.
 Annual Hospital Reports.
 Chicago Statistics—Courtesy of H. Bundesen and L. Nadelhoffer.

Contracted Pelvis

- Holland, E.: J. Obst. & Gynaec. Brit. Emp. 28: 358, 1921.
 Erving, H., and Power, H.: AM. J. OBST. & GYNEC. 46: 395, 1943.
 King, E.: AM. J. OBST. & GYNEC. 35: 482, 1938.

Placenta Previa

- Mackenzie, L.: AM. J. OBST. & GYNEC. 33: 577, 1937.
 Irving, F.: AM. J. OBST. & GYNEC. 32: 36, 1936.
 Findley, D.: AM. J. OBST. & GYNEC. 36: 267, 1938.
 Davis, M.: AM. J. OBST. & GYNEC. 32: 518, 1936.
 Berkeley, C.: J. Obst. & Gynaec. Brit. Emp. 43: 393, 1936.
 Kellogg, F.: M. Rec. & Ann. 37: 502, 1943.
 Watson, B., and Gusberg, S.: AM. J. OBST. & GYNEC. 46: 524, 1943.
 Reyeroft, F., and Platz, C.: AM. J. OBST. & GYNEC. 44: 509, 1942.

Rupture of Uterine Scar

- Bannister, J.: Brit. M. J. 2: 1143, 1935.
 Holland, E.: J. Obst. & Gynaec. Brit. Emp. 28: 488, 1921.
 Bill, A., Barney, W., and Melody, G.: AM. J. OBST. & GYNEC. 47: 712, 1944.
 Schwarz, O., and Paddock, R.: AM. J. OBST. & GYNEC. 36: 962, 1938.

Constriction Rings

- McKenzie, C.: AM. J. OBST. & GYNEC. 33: 835, 1937.
 Rudolph, L.: J. A. M. A. 108: 532, 1937.

Postmaturity and Overweight

- Wilson, K.: New York State J. Med. 42: 883, 1942.
 Rathbun, L.: AM. J. OBST. & GYNEC. 46: 278, 1943.

Elderly Primipara

- Kuder, K., and Johnson, D.: AM. J. OBST. & GYNEC. 47: 794, 1944.
 Erving, H., and Power, H.: AM. J. OBST. & GYNEC. 46: 395, 1943.

Eclampsia—Toxemia of Pregnancy

- Dieckmann, Wm. J.: The Toxemias of Pregnancy, St. Louis, 1941, The C. V. Mosby Co.

Abruptio Placentae

- Irving, F.: Surg., Gynec. & Obst. 67: 56, 1938.
 Bland, P., and Rakoff, A.: AM. J. OBST. & GYNEC. 36: 165, 1938.
 Irving, F.: AM. J. OBST. & GYNEC. 34: 881, 1937.
 Weymeersch, A., and Snoeck, J.: Gynéc. et obst. 36: 156, 1937.
 O'Regan, J.: AM. J. OBST. & GYNEC. 46: 566, 1943.

Breech

- Walsh, J., and Kuder, J.: AM. J. OBST. & GYNEC. 47: 541, 1944.
 Goethals, T.: AM. J. OBST. & GYNEC. 37: 663, 1939.
 Ibid. 38: 105, 1939.

Fetal Mortality

- Douglas, G., and Stander, H.: AM. J. OBST. & GYNEC. 46: 1, 1943.
 Potter, E., and Adair, F.: AM. J. OBST. & GYNEC. 45: 1054, 1943.

Puerperal Infection and Morbidity

- Brown, T. K.: AM. J. OBST. & GYNEC. 38: 969, 1939.
 Mayes, H.: New York State J. Med. 43: 1518, 1943.
 Baldwin, J. F.: Tr. Sect. Obst. & Gynec., and Abd. Surg. A. M. A. 42: 96, 1929.

Follow-up Studies

- Schmelzer, F.: Zentralbl. f. Gynäk. 64: 1354, 1940.
 Bride, J.: J. Obst. & Gynaec. Brit. Emp. 28: 463, 1921.

Anesthesia

- Hingson, R.: AM. J. OBST. & GYNEC. 47: 718, 1944.
 Waters, E.: New England J. Med. 226: 380, 1942.
 Watter, L.: Am. J. Surg. 63: 348, 1943.

Discussion

DR. ROLAND S. CRON, MILWAUKEE, WISCONSIN.—This is a very masterful presentation of the cesarean section problem. It is most complete and we subscribe to its principles almost without exception.

In the matter of vaginal and rectal examination, we differ with him. We prefer to have the patient experience five or six rectal rather than one or two vaginal examinations. We do not routinely pack the uterus after cesarean section as Dr. Dieckmann advocates. The vast majority of cesarean sections in Milwaukee are done under general anesthesia. In Milwaukee only 25 per cent of all the deliveries in the State occur, while 50 per cent of all cesareans are done there.

A study of the cesarean statistics from the Milwaukee County Health Department and five large hospitals with maternity departments, during the years 1939 to 1943, inclusive, shows a marked increase in hospital deliveries so that, in 1943, 10,316 of the 11,556 deliveries were cared for in hospitals. Maternal mortality, however, in 1943, jumped to 3.3 from a previous 1.4 per 1,000 deliveries. Does this mean less satisfactory maternal care since the Armed Services have deprived us of so many obstetricians? It is also interesting to note that one-third of all maternal deaths were complicated by cesarean section. For example, during 1940 the incidence of section in Milwaukee County had reached 6.4 per cent with the very high rate of 9.4 per cent for all hospital deliveries. Realizing that too many women were being sectioned needlessly, a group of obstetricians decided to correct this situation. Accordingly, consultation by a member of the staff of each institution was demanded before operation. The results were most astounding. Without exception, the incidence in the three institutions where such a rule was adopted was immediately reduced by 50 per cent so that, during the past two years, the rate had been reduced to a low of 2.2 per cent in the County, and 9.6 per cent in a private hospital with an acceptable average of about 4.8 for the controlled group of institutions. Even with this remarkable reduction there has been no increase in fetal mortality. The maternal mortality for cesareans during the years 1940 to 1943, after consultation service had been established, showed 2 deaths in 853 cesarean sections, an incidence of 0.23 per cent. When one realizes that 40 per cent of these cesareans were done by general surgeons or practitioners, and a very high percentage done under general anesthesia, it appears that the contraindications had been observed and that the higher the incidence of sections the lower will be the mortality rate.

SERUM PROTEIN IN NORMAL AND TOXEMIC PREGNANCY*

ROBERT E. RINEHART, M.D.,† ROCHESTER, MINN.

(From the Department of Biochemistry, University of Oregon Medical School, Portland)

A LOWERED concentration of total plasma or serum protein during pregnancy has been reported by numerous investigators.¹⁻²² The study by Plass and Matthew¹⁴ is the most complete in the literature on this subject. They found that during normal pregnancy the concentration of plasma protein begins to fall during the third lunar month, or occasionally even before that time, and decreases gradually to a minimum at the ninth month. Thereafter, there is a slight rise, with values at the tenth month still somewhat below normal. A further sharp increase occurs at the time of labor but in the next forty-eight hours the concentration of protein suffers an abrupt decrease, followed by a gradual rise to normal about one week after labor. Fewer studies

*Originally submitted to the Department of Biochemistry and The Graduate Division of the University of Oregon Medical School in partial fulfillment of the requirements for the degree of Master of Science.

†Now a Fellow in Medicine of the Mayo Foundation, Rochester, Minnesota.

of protein fractions during pregnancy have been made.^{3-6, 8, 9, 13-20} Most investigators have reported that the concentration of serum albumin closely parallels that of the total serum protein and is responsible for the changes noted.

This study was undertaken because of the possible relationship between the concentration of serum protein and the mild, so-called physiologic, edema of normal pregnancy and the severe edema and albuminuria of pre-eclampsia. Strauss¹⁶⁻²⁰ has discussed this problem at length and presented a great deal of evidence indicating that many of the symptoms of eclamptogenic toxemia are initiated by a lowered concentration of serum protein.

Methods and Material

The concentration of total serum protein was determined by the colorimetric biuret method of Robinson and Hogden.²³ The albumin was separated by Kingsley's²⁴ procedure and its concentration determined in the same manner. A Klett-Summerson photoelectric colorimeter was used throughout the study. The determinations were frequently checked by Kjeldahl analysis of aliquot portions and the results were always within the limits of experimental error. Blood was drawn without stasis, allowed to coagulate, and the serum analyzed within twenty-four hours.

The average and extreme values for thirty-one healthy nonpregnant student nurses, which are considered to cover the "normal" range, were as follows: Total serum protein, average value 6.94 Gm. and extreme values 6.6 and 7.3 Gm. per 100 c.c. respectively. Albumin, average value 4.96 Gm. and extreme values 4.7 and 5.2 Gm. Globulin, average value 1.99 Gm. and extreme values 1.5 and 2.4 Gm.

The average and extreme values for thirty healthy male medical students were similar but somewhat higher. The average value for total serum protein was 7.55 Gm. and the extreme values were 6.9 and 8.6 Gm. The average value for serum albumin was 5.01 Gm. and the extreme values were 4.0 and 5.8 Gm. The average value for serum globulin was 2.47 Gm. and the extreme values were 1.6 and 3.8 Gm. The spread of the extreme values here probably represents variations in environmental factors, not encountered so often in the group of nursing students. It is quite clear, however, that the average and extreme values for men tend to be significantly higher than those for women.

Subjects were selected from the patients attending the prenatal clinic. All patients who had systemic disease accompanying pregnancy were excluded from the series. Patients included in the toxemic group were selected according to the criteria of Strauss,²⁰ which were stated as follows: "The clinical picture manifested by these women is characterized, first, by the absence of apparent abnormalities before gestation and after the puerperium, and second, by a fairly typical course. In the last trimester of pregnancy a rapid gain in weight, generally but not always manifest as edema, is followed by a rising blood pressure, albuminuria, gastric pain, convulsions, and coma."

All dates were calculated from the actual date of delivery when this could be ascertained; in a few cases the date of expectancy was used.

For convenience the data have been classified on the basis of parity, season, and degree of toxemia. They further are subdivided under total protein, albumin, and globulin. The value for fibrinogen was not determined.

Normal Pregnancy

A total of 251 determinations of the concentration of total serum protein was made on seventy-nine normal pregnant women. Table I

TABLE I. SERUM PROTEIN VARIATIONS DURING NORMAL PREGNANCY

PERIOD	DETERMINATIONS	TOTAL SERUM PROTEIN, GM. PER 100 C.C.		SERUM ALBUMIN, GM. PER 100 C.C.		SERUM GLOBULIN, GM. PER 100 C.C.	
		RANGE	AVERAGE	RANGE	AVERAGE	RANGE	AVERAGE
Postpartum, days							
Delivery	23	5.7 to 7.5	6.8	3.7 to 5.3	4.4	1.7 to 3.2	2.4
to 20*	48	5.9 to 7.5	6.6	3.5 to 4.7	4.0	1.6 to 3.4	2.5
21 to 40	34	6.0 to 7.7	6.5	3.7 to 5.3	4.2	1.4 to 3.0	2.2
41 to 60	31	5.9 to 7.2	6.5	3.7 to 4.6	4.0	2.1 to 3.1	2.4
61 to 80	25	6.0 to 7.5	6.6	3.6 to 4.6	4.2	1.9 to 3.5	2.5
81 to 100	18	5.8 to 7.7	6.5	3.6 to 4.7	4.3	1.0 to 3.1	2.4
101 to 120	10	5.9 to 7.4	6.7	3.4 to 4.8	4.3	1.8 to 3.1	2.4
121 to 140	11	6.2 to 7.3	6.6	3.8 to 5.3	4.4	1.5 to 2.7	2.2
141 to 160	10	5.9 to 7.5	6.6	4.1 to 5.2	4.4	1.7 to 2.5	2.2
161 to 180	10	6.1 to 7.3	6.6	4.0 to 4.7	4.4	1.2 to 2.9	2.2
181 to 200	10	6.1 to 7.7	6.7	4.2 to 5.3	4.6	1.8 to 2.5	2.2
201 to 220	14	6.1 to 7.4	6.7	3.8 to 5.8	4.7	1.6 to 2.6	2.2
221 to 250	8	6.5 to 7.3	7.0	4.5 to 5.0	4.7	2.0 to 2.8	2.3
Total 251		Average	6.7	Average	4.4	Average	2.3

*Days prepartum.

TABLE II. SEASONAL VARIATIONS IN CONCENTRATION OF SERUM PROTEIN DURING NORMAL PREGNANCY

PERIOD	DETERMINATIONS	TOTAL SERUM PROTEINS, GM. PER 100 C.C.		SERUM ALBUMIN, GM. PER 100 C.C.		SERUM GLOBULIN, GM. PER 100 C.C.	
		RANGE	AVERAGE	RANGE	AVERAGE	RANGE	AVERAGE
Dec.-Jan.-Feb.	12	6.7 to 7.8	7.3	4.6 to 5.7	5.0	1.0 to 3.1	2.3
Mar.-Apr.-May	114	6.0 to 7.5	6.6	3.5 to 5.1	4.2	1.7 to 3.4	2.4
June-July-Aug.	109	5.5 to 7.5	6.6	3.4 to 5.8	4.3	1.3 to 3.5	2.3
Sept.-Oct.-Nov.	43	6.0 to 7.5	6.8	3.6 to 5.0	4.3	1.7 to 3.4	2.5
Total 278							

shows the variations observed in this group. It will be noted that the average value for globulin remained almost constant throughout. At all times it was slightly higher than that for normal nonpregnant women. The concentration of total serum protein tended to fall to a minimum during the eighth and ninth months but rose rapidly toward normal after delivery. The values ranged between 5.7 and 7.7 Gm. per 100 c.c.; the average value was 6.7 Gm. The lowest average value represented a decrease of 7.1 per cent from the average for nonpregnant women, compared with a 9.3 per cent decrease noted by Plass and Matthew.¹⁴ The most marked changes were found in the albumin fraction. The concentration of albumin fell from an average of 4.7 Gm. per 100 c.c. of serum at the beginning of the study (average normal value for nonpregnant women 4.9 Gm.) to 4.0 during the eighth and ninth months, a decrease of 18 per cent from the average normal value for nonpregnant women. Plass and his associates^{13, 14} found a decrease of 13.5 per cent in this fraction. In the thirty-one nonpregnant women studied, the albumin constituted 72 per cent of the total protein, whereas at its lowest point in the pregnant series it constituted 62 per cent, a decrease of 14 per cent.

Since it seemed that the concentration of serum protein might be

related to the parity of the subjects, the values obtained for the primiparas in the series were plotted separately. The curves obtained coincided almost exactly with those plotted for the entire group. The concentration of serum protein, expressed in grams per 100 c.c., were as follows: total protein, average 6.7, range 5.8 to 7.7; albumin, average 4.4, range 3.6 to 5.9; globulin, average 2.3, range 1.0 to 3.1.

Since it has been shown by Dodd and Minot²⁵ that the concentration of serum protein of persons in a given geographical region tends to vary with the season, the values were replotted according to the month in which the specimens were taken, without regard for the duration of the pregnancy. These are shown in Table II. It is obvious that, with the exception of the period December-January-February, the seasonal average was nearly constant. The small number of determinations in the group mentioned decreases the significance of the apparently increased value for total serum protein and serum albumin observed.

Toxemic Pregnancy

In the five cases of pre-eclampsia studied, a regrettably small number, the changes in the concentration of serum protein were the greatest observed in the entire series. If it were not that these findings agree so well with those reported by Eufinger,⁸ Plass and his associates,^{13, 14} Eastman,⁶ and Strauss,¹⁶⁻²⁰ one would be inclined to minimize their significance because of the paucity of cases. The values are recorded in Table III. The values for serum protein, expressed in grams per 100 c.c., shortly before and at delivery were as follows: total protein, average 5.6, range 4.8 to 6.4; albumin, average 3.5, range 3.0 to 4.0; globulin was not calculated since the values did not differ appreciably from those in normal pregnancy. The fall in the value for total protein from the average value obtained in normal nonpregnant women was 19 per cent, the fall in albumin according to the same standard was 33 per cent. The value for total protein was 14 per cent lower, and that for the albumin fraction 12 per cent lower than the lowest average values obtained at any time during normal pregnancy. In these cases the albumin constituted 62 per cent of the total protein, giving an albumin:globulin ratio of 1.65. Case 4, which showed the least lowering of the albumin and total protein, was the mildest of the five cases observed.

CASE 1.—The patient was an 18-year-old primipara with a generally contracted pelvis. There was no history of renal disease or any familial history of hypertension. The pregnancy progressed without incident until the eighth lunar month, at which time there were rapid increase in weight, albuminuria, headache, generalized edema, and epigastric pain. While the patient was on a low salt diet in the hospital the visible edema receded and there was no further gain in weight. The blood pressure, however, steadily rose from 120/68 at the onset of her symptoms to 145/100 in the ninth month, at which level it remained until term. After a trial at labor, a normal infant was delivered by low cervical section. The blood pressure dropped within twenty-four hours after delivery to 120/60 and remained there during her stay in the hospital. A mild degree of albuminuria persisted after delivery. The patient has not returned since she left the hospital.

CASE 2.—The patient was a 19-year-old primipara with no physical abnormalities. There was no history of renal disease or familial hyper-

TABLE III. CONCENTRATION OF SERUM PROTEIN IN TOXEMIC PREGNANCY

DAYS	SERUM PROTEIN, GM. PER 100 C.C.			REMARKS
	TOTAL	ALBUMIN	GLOBULIN	
Case 1				
6 a.p.	5.2	2.7	2.5	Gained 6 lb. in one wk.; B.P. 120/68
1 a.p.	5.2	2.6	2.6	Headache, generalized edema; B.P. 145/100;
3 p.p.	4.8	3.8	1.0	low cervical section
8 p.p.	7.0	4.9	2.1	Asymptomatic B.P. 120/60
26 p.p.	7.2	4.5	2.7	Asymptomatic B.P. 120/60
Case 2				
19 a.p.	6.7	4.3	2.4	B.P. 150/100; otherwise normal
4 a.p.	5.4	4.3	1.0	B.P. 140/95; albuminuria, grade 3 plus
2 a.p.	5.6	3.4	2.2	Spontaneous labor, premature; B.P. dropped
				from 160/100 to 120/80 in 24 hr.
3 p.p.	5.3	3.3	2.0	No further pertinent data available
7 p.p.	6.5	3.7	2.8	
11 p.p.	6.1	3.9	2.3	
Case 3				
70 a.p.	6.7	4.2	2.6	
39 a.p.	6.6	4.2	2.4	
17 a.p.	6.0	3.7	2.3	B.P. 152/100; moderate edema; patient hos-
				pitalized
10 a.p.	6.1	3.9	2.1	Headache and epigastric pain
2 a.p.	6.1	3.6	2.5	Forceps delivery, B.P. 140/108
1 p.p.	5.7	3.4	2.4	
4 p.p.	6.1	3.9	2.2	B.P. 122/80; asymptomatic
9 p.p.	6.4	4.0	2.4	B.P. 122/80; asymptomatic
Case 4				
161 a.p.	7.3	4.7	2.6	Blood pressure was labile throughout preg-
140 a.p.	6.4	4.2	2.3	nancy. Patient entered hospital 18 days
119 a.p.	6.4	4.3	2.1	before delivery, with B.P. 138/90 and mild
98 a.p.	6.1	3.6	2.4	pitting edema. Delivered spontaneously
77 a.p.	7.0	4.8	2.2	without difficulty. B.P. 175/80 with occa-
56 a.p.	6.5	4.4	2.0	sional albuminuria. Clinically, a very mild
36 a.p.	6.9	4.0	2.9	case of pre-eclampsia
11 a.p.	5.9	3.6	2.4	
3 a.p.	6.1	4.0	2.2	
5 p.p.	6.4	4.2	2.2	
Case 5				
37 a.p.	6.6	4.0	2.6	
30 a.p.	6.8	3.9	2.9	B.P. gradually increased to 126/88
27 a.p.	6.6	3.5	3.1	
21 a.p.	6.4	4.0	2.4	Albuminuria, grade 2 to 3 plus; B.P. 140/90
4 a.p.	5.3	3.1	2.2	Semicomatose, very edematous
1 a.p.	5.5	3.1	2.4	Semicomatose, very edematous
2 p.p.	5.3	3.0	2.3	B.P. 126/86; no albuminuria; symptom-
				atically much better
7 p.p.	6.4	3.4	3.0	
11 p.p.	6.1	3.4	2.7	
17 p.p.	6.8	4.0	2.8	Continued to have albuminuria, grade 1 plus
a.p. = antepartum; p.p. = postpartum.				

a.p. = antepartum; p.p. = postpartum.

tension. She was perfectly well until late in the seventh lunar month, at which time a feeling of discomfort developed in the upper part of the abdomen and was accompanied by a mild degree of generalized edema. At this time her blood pressure was 108/68. There was no albuminuria. She was next seen early in the ninth lunar month, at which time her blood pressure had risen to 150/100 and there was moderate albuminuria. She was placed on a salt-free diet; rest in bed was advised and mild sedation was prescribed at home. After two weeks of this regimen, her blood pressure dropped to 130/90 but the other symptoms remained unchanged. During the next week her blood

pressure rose to 140/95. There was no generalized edema, but there was severe albuminuria. She was hospitalized, and after five days, with no change in her symptoms, premature labor occurred spontaneously. At this time the value for the urea nitrogen was 16 mg. per 100 c.c. of blood. The value for the carbon dioxide combining power of the blood plasma was 72 volumes per cent, that for the blood sugar was 132 mg. per 100 c.c. of blood, and the value for the plasma chloride was 480 mg. per 100 c.c. Her blood pressure immediately dropped to 120/80 from 160/100 and remained at that level. Ten days after delivery the value for the urea nitrogen was 20 mg. per 100 c.c. of blood and the urea clearance, maximal, was 73.4 per cent of normal. When she was dismissed from the hospital eighteen days after delivery, slight albuminuria was present. She has not returned.

CASE 3.—The patient was an 18-year-old primipara with no physical abnormalities. There was no history of renal disease or familial hypertension. Her pregnancy progressed normally until early in the ninth lunar month, at which time her blood pressure rose from a normal level to 152/100. Headache and epigastric pain developed and there was a rapid gain in weight accompanied by generalized edema. At no time did she have any great degree of albuminuria. The blood pressure varied between 168/100 and 140/108 after a five-day period of hospitalization on the recommended regimen. Because of the persistent hypertension she was medically stimulated and delivered of a normal infant. Shortly before delivery the value for the urea nitrogen was 11 mg. per 100 c.c. of blood and that for the blood sugar was 68 mg. per 100 c.c. After delivery, the blood pressure dropped to 122/80 and the other symptoms disappeared.

CASE 4.—The patient was a 22-year-old primipara with no physical abnormalities. There was no history of renal disease. Her mother had hypertension. Throughout the entire pregnancy, the blood pressure was labile and varied over a wide range at hourly intervals. She had no albuminuria at any time and no systemic symptoms. She was hospitalized late in the ninth lunar month because of a blood pressure of 138/90. After rest in bed on the recommended regimen for three days, the blood pressure dropped to 120/80, but in view of the previous fluctuations little significance can be attached to this. She signed her own release, against the advice of the physician, after a short period of hospitalization. After a few days, she entered the hospital again in active labor with a blood pressure of 175/80. Albuminuria varied from mild to moderate during the week immediately preceding and following delivery. Shortly before delivery the dilution and concentration test was normal, in spite of the use of a low salt diet, and at the same time the urea clearance was 69 per cent of normal. When she was dismissed from the hospital, her blood pressure was 120/80, and albuminuria was not present.

CASE 5.—The patient was a 30-year-old primipara with no physical abnormalities. There was no history of renal disease or familial hypertension. Throughout pregnancy there was a gradual increase in the diastolic pressure from 120/74 during the third month to 126/88 early in the ninth month. During the eighth and ninth months there was a moderate to severe degree of albuminuria. Her weight increased very rapidly during this period and severe generalized edema developed. At its maximum, shortly before delivery, the blood pressure was 160/96, but rapidly fell to 126/76 after delivery. Labor was induced a little before full term by rupture of the membranes. She continued to have mild albuminuria for two months after delivery, after which the urine became normal.

Serum Protein in Blood of Cord

In so far as is known, no one has studied the concentration of serum protein in maternal blood and blood of the umbilical cord at the time of delivery. Because of the availability of material during the period in which the preceding studies were being made, rather than with the hope of obtaining any significant information, thirteen determinations of this type were made. The maternal blood was obtained by the usual method, immediately after delivery of the child. The blood of the cord was obtained immediately after the second stage of labor. The data are presented in Table IV.

TABLE IV. CONCENTRATION OF SERUM PROTEIN OF MATERNAL BLOOD AND BLOOD OF CORD AT THE TIME OF DELIVERY

CASE	SERUM PROTEIN, GM. PER 100 C.C.					
	MATERNAL BLOOD			BLOOD OF CORD		
	TOTAL	ALBUMIN	GLOBULIN	TOTAL	ALBUMIN	GLOBULIN
1	6.6	4.4	2.2	6.6	4.5	2.1
2	7.2	4.7	2.5	7.0	4.7	2.3
3	6.4	4.1	2.3	6.3	4.2	2.1
4	6.6	4.1	2.5	6.4	4.4	2.0
5	6.8	4.4	2.5	6.1	4.1	2.0
6	6.2	4.4	1.8	5.5	3.8	1.7
7	6.3	4.3	2.0	6.0	4.3	1.7
8	7.1	3.9	3.2	6.3	3.6	2.7
9	6.9	3.9	3.0	6.5	3.9	2.6
10	6.4	3.9	2.5	5.8	3.9	1.9
11	6.0	4.3	1.7	6.5	4.6	1.9
12	5.8	3.8	2.0	6.0	4.3	1.7
13	6.6	4.2	2.4	6.6	4.3	2.3
Average	6.5	4.2	2.3	6.3	4.2	2.1

The individual determinations showed some variation, usually an increase in total protein and globulin in the maternal blood. The values for albumin were nearly the same in both maternal and cord blood, and when the series was averaged they were exactly the same. The occurrence of a lower level of globulin in most specimens of blood of the cord may be ascribed to the known deficiency of antibodies in the newborn infant. The most remarkable feature of the whole series is the close correlation between the albumin in the fetal and maternal blood, indicating that a delicate osmotic balance is maintained across the placenta.

Comment

Within the past few years it has been shown that the liver is the principal organ in the body concerned with the manufacture of serum albumin. The evidence supporting this has been thoroughly reviewed by Whipple and Robscheit-Robbins.²⁶ Numerous investigators, including Kaufmann,^{27, 28} Botella-Llusia,²⁹ Neuweiler,^{30, 31} Cross,³² Hirschheimer,^{33, 34} Sullivan and his associates,³⁵ and Hofbauer³⁶ have studied the function of the liver with a variety of tests during pregnancy. They all found that the ability of the liver to synthesize or dispose of various substances is markedly impaired during the latter part of pregnancy, and even more so in toxemic pregnancy. The curve of liver function during pregnancy roughly follows that of the serum albumin, both being depressed during the latter months. Hofbauer, after an extensive study of the changes in the blood during pregnancy, concluded: "The latent liver damage of pregnancy is directly related to the known changes in the blood: In-

crease in the sedimentation rate, changes in the acid-base relationship, changes in colloid stability, increase of globulin, decrease of surface tension, hemoclastic crises." It may develop that the hormonal changes associated with pre-eclampsia are due to an impaired metabolism of these substances in the liver.

It is the opinion of an increasing number of investigators that many, if not all, of the manifestations of true eclamptogenic toxemia may be explained on the basis of a disturbance in protein metabolism. Obviously there must be predisposing factors present in the maternal organism and its environment or eclampsia would be more prevalent than it is. Some of these factors may be as follows:

1. Multiple pregnancy, polyhydramnios, or hydatid mole, causing a rapid increase of intra-abdominal pressure and interfering with the portal circulation and absorption of metabolites from the intestine.

2. A diet deficient in protein, unable to supply the needs of both the mother and the fetus.

3. Restriction of food and fluid plus parenteral administration of salt solution, as advocated in certain therapeutic regimens.

4. Anatomic abnormalities of the abdominal viscera or bony pelvis, disturbing the abdominal circulation as in 1.

Summary and Conclusions

Two hundred fifty-one determinations of the serum protein of seventy-nine normal pregnant women and thirty-nine determinations on five pre-eclamptic women were made. The average value for serum globulin remains almost constant throughout normal and toxemic pregnancies. During the normal pregnancy the average value for the total protein tends to fall from the nonpregnant level to a minimum during the eighth to ninth month and to rise rapidly to normal after delivery. At its lowest point this represents a decrease of 7.1 per cent from the nonpregnant average. This decrease in the concentration of total protein is confined primarily to the albumin fraction. The albumin decreased from a nonpregnant average value of 4.9, to 4.0 Gm. per 100 c.c., a fall of 14 per cent. The average value for total protein in pre-eclampsia was 14 per cent below that of normal women in the same stage of pregnancy. This decrease in total protein is confined to the albumin fraction. It was 12 per cent lower than the lowest average value obtained at any time during normal pregnancy, and 33 per cent lower than the average for normal nonpregnant women. The probable dependency of these changes on known alterations of the function of the liver during pregnancy has been considered. A total of fifteen determinations of the serum protein in simultaneously drawn maternal blood and blood of the cord was made. The albumin content of maternal serum and serum of the cord is nearly identical; a slight difference is noted in the globulin fraction.

References

1. Bergmann, Erich: *Zentralbl. f. Gynäk.* 48: 1346, 1924.
2. Bibb, J. D.: *AM. J. OBST. & GYNEC.* 42: 103, 1941.
3. Coetzee, L. J.: *Proc. Roy. Soc. Med.* 18: 28, 1924.
4. Dieckmann, W. J., and Wegner, C. R.: *Arch. Int. Med.* 53: 353, 1934.
5. Dienst: *Arch. f. Gynäk.* 109: 669, 1918.
6. Eastman, N. J.: *AM. J. OBST. & GYNEC.* 19: 343, 1930.

7. Eckelt, Kurt: *Ztschr. f. Geburtsh. u. Gynäk.* 81: 1, 1919.
8. Eufinger, Heinrich: *Klin. Wehnschr.* 7: 492, 1928.
9. Eufinger, Heinrich: *Arch. f. Gynäk.* 133: 452, 1928.
10. Landsberg, Erich: *Arch. f. Gynäk.* 92: 693, 1910.
11. Mahnert, Alfons: *Arch. f. Gynäk.* 114: 168, 1921.
12. Mudaliar, A. L., Nayar, A. S. M., and Menon, M. K. K.: *J. Obst. & Gynaec. Brit. Emp.* 47: 291, 1940.
13. Plass, E. D., and Bogert, L. J.: *Bull. Johns Hopkins Hosp.* 35: 361, 1924.
14. Plass, E. D., and Matthew, C. W.: *AM. J. OBST. & GYNEC.* 12: 346, 1926.
15. Ruzsnyák, S., Barát, I., and Kürthy, L.: *Ztschr. f. klin. Med.* 98: 337, 1924.
16. Strauss, M. B.: *Am. J. M. Sc.* 190: 811, 1935.
17. Strauss, M. B.: *Am. J. M. Sc.* 194: 772, 1937.
18. Strauss, M. B.: *Am. J. M. Sc.* 195: 723, 1938.
19. Strauss, M. B.: *Am. J. M. Sc.* 196: 188, 1938.
20. Strauss, M. B.: *AM. J. OBST. & GYNEC.* 38: 199, 1939.
21. Zangemeister, W., and Meissl, T.: *München. med. Wehnschr.* 50: 673, 1903.
22. Zangemeister, W.: *Ztschr. f. Geburtsh. u. Gynäk.* 49: 92, 1903.
23. Robinson, H. W., and Hogden, Corinne G.: *J. Biol. Chem.* 135: 727, 1940.
24. Kingsley, G. R.: *J. Biol. Chem.* 133: 731, 1940.
25. Dodd, Katharine, and Minot, A. S.: *J. Pediat.* 8: 452, 1936.
26. Whipple, G. II., and Robscheit-Robbins, F. S.: *J. Exper. Med.* 76: 283, 1942.
27. Kaufmann, C.: *Ztschr. f. Geburtsh. u. Gynäk.* 99: 382, 1931.
28. Kaufmann, C.: *Klin. Wehnschr.* 11: 493, 1932.
29. Botella-Llusia, J.: *Arch. f. Gynäk.* 161: 254, 1936.
30. Neuweiler, W.: *Klin. Wehnschr.* 19: 135, 1940.
31. Neuweiler, W.: *Klin. Wehnschr.* 18: 1050, 1939.
32. Cross, R. C.: *AM. J. OBST. & GYNEC.* 18: 800, 1929.
33. Hirsheimer, A.: *AM. J. OBST. & GYNEC.* 29: 395, 1935.
34. Hirsheimer, A.: *AM. J. OBST. & GYNEC.* 37: 363, 1939.
35. Sullivan, C. F., Tew, W. P., and Watson, E. M.: *J. Obst. & Gynaec. Brit. Emp.* 41: 347, 1934.
36. Hofbauer, J.: *Zentralbl. f. Gynäk.* 57: 35, 1933.

THE TREATMENT OF FUNCTIONAL DYSMENORRHEA WITH PREGNENINOLONE

FLOYD E. HARDING, M.D., LOS ANGELES, CALIF.

(From the Department of Endocrinology, Ross-Loos Medical Group)

FUNCTIONAL or primary dysmenorrhea is a very puzzling condition that frequently does not respond to therapy. It results in much suffering and loss of time by the patient. A simple, harmless, and effective method of treatment is, therefore, greatly needed. With this in mind, patients have been observed following the oral use of pregnenolone.

Pregnenolone, synthesized in 1938,^{14, 36} is a crystalline substance that differs only slightly from progesterone. There is the substitution of OH for H in the 17-position and subtraction of H₂O from the side chain. Hence, it is sometimes called anhydroxy-oxyprogesterone and it has been shown to have essentially the same clinical effect as progesterone. There is, however, at least one great difference—it is effective when administered orally.

When progesterone became available for clinical use, it replaced the corpus luteum preparations. The early corpus luteum extracts were ineffective because they contained no appreciable amount of active substance.

Although progesterone was quite generally used from 1935 to 1940, its therapeutic indications were rather obscure. Clinicians, who had

observed the effects of progesterone on women with uterine pain, reported that some of the patients were free from pain when it had been given.^{5, 6} Thus, progesterone seemed to be definitely indicated for dysmenorrhea.^{18-20, 25}

Following this general observation, gynecologists attempted to find a type of dysmenorrhea for which progesterone would be specific. This work failed in its purpose, but some interesting facts were established as a result of this and other research. First, progesterone changed the endometrium from an estrogenic (proliferative) to a progestational (secretory) type in human beings as well as in animals.^{2, 10} Second, uterine biopsy showed that most patients with dysmenorrhea bled from a progestational endometrium.³ When abnormality occurred, however, underdevelopment of the endometrium was more common than overdevelopment.^{23, 24} Third, there was no agreement as to whether dysmenorrhea patients with anovulatory menstruation were benefited more by progesterone therapy than dysmenorrhea patients with menstruation following ovulation. Also, it was claimed that patients had no pain when anovulatory menstruation was produced with large doses of estrogens.^{9, 12, 21} Fourth, urine assays for pregnandiol, a substance derived from progesterone, would be of no value in dysmenorrhea even though they might be a guide to diagnosis of anovulatory menstruation.^{3, 4, 8}

How is the pain relieved with progesterone? Animal experiments were made, showing that progesterone inhibits uterine contractions which ordinarily follow injections of pituitrin. Based on this fact and the observed clinical action of the corpus luteum hormone in preventing spontaneous abortion, progesterone was considered a uterine inhibitor, that is, an antagonist of estrogen.^{16-18, 26}

This mechanism of relief of pain has been questioned, however, and other theories, too numerous to mention here, have been suggested.^{1, 11, 13, 22, 28, 31, 32} Since the cause of pain may have nothing to do with uterine contractions, settling the dispute as to whether progesterone increases or decreases them is of little clinical aid. It is known, however, that uterine cramps increase in the premenstrual period when estrogen and progesterone are increased, but during pregnancy, when they are greatly increased, the uterine cramps are inhibited.

It cannot be said positively that functional dysmenorrhea is caused by endocrine disease, but endocrine function is at least a contributing factor. Treatment with estrogen,^{9, 12, 29, 30} progesterone,^{20, 25, 33} and testosterone²⁷ changes the type and amount of menstruation, length of menstrual cycle, and amount of menstrual pain.

The action of pregnenolone is very similar to that of progesterone.^{15, 37} It has been suggested, however, that pregnenolone may be more effective for the relief of dysmenorrhea than progesterone.³

The papers previously published on the use of pregnenolone for functional dysmenorrhea have shown it to be beneficial.^{3, 7, 34, 35}

Patients Studied

Of the eighty-two patients treated, thirty-one were single and fifty-one married. They were in the following age groups:

Age	11-20	21-30	31-40	41-50	51-60
No. of patients	17	33	25	6	1

Fifty-five women, twenty-four of whom were married, had no children. Twenty-seven women had children. There were forty-two children in all. Menstruation began at the following ages:

Age	10	11	12	13	14	15	16	17
No. of patients	4	16	29	17	10	3	2	1

The patients in this group were more neurotic than an equal number of individuals picked at random. The dysmenorrhea was of long standing in the great majority of patients, the date of onset ranging from the beginning of puberty to five years before the initiation of the present treatment. Pelvic examinations were essentially negative, and all cases were diagnosed as functional dysmenorrhea. The patients were referred to the endocrine department by other physicians. Nearly all the patients had been given one or more types of medical or surgical treatment. Most of them had had endocrine injections. None of the patients were satisfactorily relieved by nonnarcotic analgesics. It was believed that previous treatment would largely rule out psychological response to the treatment with pregnenolone.

Method of Treatment

The pregnenolone* was administered orally in 5 mg. tablets. The daily dose was 5 mg. in sixty-nine patients, 10 mg. in twelve patients, and 15 mg. in one patient.

Days during which the tablets were given	No. of patients
14th day of cycle until menstruation started	5
18th day of cycle until menstruation started	52
20th day of cycle until menstruation started	1
21st day of cycle until menstruation started	4
23rd day of cycle until menstruation started	1
24th day of cycle until menstruation started	1
18th day of cycle until pain had lessened	18

The days were counted from the first day of the last menstruation.

No other treatment for dysmenorrhea was administered during the treatment with pregnenolone. Tablets for pain were not prescribed, and the patient was instructed to report for advice if pain occurred.

Results With Pregnenolone

Eighty-two patients with dysmenorrhea were treated with pregnenolone tablets. There was 50 per cent or more improvement in sixty patients and less than 50 per cent improvement in twenty-two patients. Thus, the treatment was considered satisfactory for 73 per cent of the patients. Six patients were classified as worse because there was more pain during the months treated. Two patients became pregnant and did not menstruate after taking the tablets. Table I shows the average percentage of improvement during the months treated. This percentage was based on the amount of pain estimated by the patient and her relatives, the request for pain-relieving therapy and the amount required, the length of time the patient was bedridden or unable to work, her general appearance, etc.

TABLE I. PREGNENOLONE TREATMENT OF FUNCTIONAL DYSMENORRHEA

Improvement in %	Worse	0	25	35	50	65	75	85	90	100	Pregnant
No. of patients	6	11	3	2	11	4	15	4	6	18	2

*The pregnenolone (Pranone) was obtained from the Schering Corporation, Bloomfield, New Jersey.

The prevention of pain was considered to be temporary as the patients were usually only benefited in the month that medication was taken. A follow-up of these patients, however, showed that occasionally the pain did not return for two or three months after the tablets were discontinued. A few patients were seen six months to a year later, and the dysmenorrhea had not returned. Some patients also stated that while the pain became worse when treatment was stopped, it did not become as bad as it was before treatment had been given. Frequently, the duration of pain was cut down one, two, or three days. There was some variation in the amount of pain from month to month while taking the tablets, and a few patients claimed that the pain was present some months and not others. In these patients the pain might occur the first month or any succeeding month.

Other severe symptoms associated with dysmenorrhea were prevented in the following instances: vomiting, 5; nausea, 6; diarrhea, 1; and dizziness, 2. One patient had relief of vomiting without relief of pain. Many of the other patients had mild gastrointestinal symptoms which were relieved if the pain was relieved, and vice versa. There was no relief from severe nausea in two patients. Premenstrual tension was relieved in a few patients.

Most of the patients felt "no different" while they were taking the tablets, but a few felt better and the effect appeared to be similar to that observed with the use of stimulants. This improvement was different from the "tonic effect" noted with the use of estrogens. It was described by Hamblen and his associates⁴ as a "mild euphoria."

Periodic pain frequently was detrimental to the physical and mental well-being of these patients. When the pain was prevented by the taking of a few tablets, the patient experienced a sense of security and confidence, and no longer feared that the condition might become worse or the pain and other symptoms unbearable. In subsequent months the nervousness subsided; some gained weight; and others looked better, had a better color, and appeared more rested.

Effects Upon Menstruation

Before treatment the menstruation was essentially regular in thirty-nine patients and irregular in forty-one patients. Thirty-one patients were usually late, twenty-seven on time, thirteen early, and nine mixed (late and early). Data were not obtained from two patients.

The figures in Table II show that with the method used there was a tendency for pregnenolone to cause earlier menstruation except when menstruation was quite early before treatment. There was no change in the amount of flow in three-fourths of the patients regardless of whether the pretreatment menstruation was heavy, scanty, or normal; but when a change occurred, the heavy periods usually became lighter, and vice versa. Two patients with excessive menstruation, however, bled very much more heavily following treatment. There was no change in the duration of flow in about three-fourths of the patients regardless of type, but when a change did occur the longer periods became shorter and vice versa. The menstrual changes that occurred with treatment were usually an improvement except for the normal twenty-seven- or twenty-eight-day cycle that was shortened.

Where early menstruation had been caused in previous months by the tablets, starting the use of pregnenolone later in the cycle, on the twentieth to the twenty-fourth day, prevented the onset of menstruation before the twenty-eighth day.

It must be kept in mind that small doses were used in this study. Larger doses would have produced greater changes in menstruation and in some instances would have caused a different response. Giving the tablets during other parts of the cycle would also have made a difference.

TABLE II. MENSTRUAL CHANGES AFTER TREATMENT

	NO. OF PATIENTS
1. <i>Change of Cycle</i>	
Earlier menstruation (before treatment 30 had been late, 9 on time, 3 mixed, and 1 early)	43
Later menstruation (before treatment 8 had been early, 4 on time, and 2 mixed)	14
Same length of cycle (before treatment 14 had been on time, 4 early, 4 mixed, and 1 late)	23
2. <i>Amount of Flow</i>	
Less in amount (before treatment 7 were excessive and 2 normal)	9
More in amount (before treatment 6 were scanty, 2 excessive, and 1 normal)	9
Same amount	62
3. <i>Duration of Flow</i>	
Shorter duration (these were seven or more days long before treatment)	11
Longer duration (before treatment 3 patients had one- or two-day periods and 6 had three- day periods)	13
Same duration	56

The length of cycle and duration of each period were considered to be accurate because each patient kept this record on a card* containing one year of twenty-eight-day cycles. Estimation of the amount of flow, of course, was dependent on the patient's judgment, and was therefore less accurate.

Reactions

The use of pregnenolone for seven to ten days before menstruation was considered harmless with the dosage used. There was no evidence of pituitary inhibition. It apparently had no effect upon the ovary, but there was a definite effect upon the uterus.

Two patients felt "keyed up" from the tablets. Nausea and vomiting occurred at menstruation in one patient who never had had these symptoms with her periods. There were no other reactions.

Results With Progesterone Injections

Twenty patients were given injections of progesterone in doses of 5 mg. to 15 mg. during the time that the patient complained of severe pain. The results of this treatment were disappointing, and as very little relief was obtained, this method was discontinued.

Later, twenty-two patients were given progesterone injections between menstrual periods. The dose ranged from 1 mg. to 5 mg. Eleven patients were treated all month while the other eleven were treated during the last two weeks of the cycle. Three patients were treated daily, but the others were treated two or three times a week. The following results were obtained: no better, 9; slight improvement, 2; 50 per cent improvement or better, 4; and 100 per cent improvement, 5. Four patients became pregnant during treatment, two the first month and two after a few months. These last two had just as severe dysmenorrhea during treatment as before. One pregnant patient had been previously considered sterile. A patient who always menstruated regularly every twenty-eight days menstruated every fourteen days for four periods while treatment was given all month. With the method used,

*Supplied through the courtesy of Mead Johnson & Co., Evansville, Ind.

this treatment was not as beneficial as the oral use of pregnenolone. Therefore, these injections were discontinued because they caused too much inconvenience and were too expensive for a treatment usually giving temporary relief.

The older case records between 1930 and 1935 were reviewed, and it was found that forty-seven patients had been treated with injections of corpus luteum twice a week throughout the menstrual cycle. Results were generally poor with this treatment. It was believed that corpus luteum injections with the material used were without value because they contained negligible quantities of progestins, and that any improvement was due to other factors. When improvement was noticed, it was usually found in milder cases and those of short duration without previous treatment. There was rarely any improvement in the patient whose pain began with the first menstrual period of puberty and in the patient where numerous other methods of treatment had been used without success. This latter type of patient with long-standing dysmenorrhea, however, was frequently benefited with pregnenolone.

Discussion

There were many advantages with pregnenolone therapy. The oral method saved the time of both the patient and the doctor. Numerous trips to the office were required for injections of progesterone but were unnecessary when tablets of pregnenolone were given. This decrease in office calls was especially important during the war because of lack of transportation. Local reactions from injections were eliminated by oral treatment. Most of the patients would not come for daily injections of progesterone, whereas, there was no objection to taking the tablets daily. The cost of daily injections was frequently prohibitive or impractical; but when the tablets were purchased in quantities of 100 or more, the cost of six to ten days' treatment was much less. Absenteeism due to dysmenorrhea was cut one day to two weeks. As a large percentage of these patients were employed, this amounted to a considerable saving of money from wages otherwise lost. Also, keeping the patient at work cut down loss of production in war plants and was responsible for more efficient service elsewhere. When successful, this method was certainly to be preferred to surgery or other more complicated and expensive measures.

There were no disadvantages except that improvement was usually temporary and did not occur in all patients. In rare instances menorrhagia was increased.

The effective dose in this series was only 5 mg. per day for ten days prior to menstruation, whereas Soule⁷ used 60 mg. per day for five days prior to menstruation. Greenblatt and his associates³ found that 5 mg. to 10 mg. for the twelve days before menstruation was effective. It was surprising that a therapeutic result was obtained with such small doses. Results with injection therapy would make it seem that larger doses were needed orally.

To be successful, treatment had to be given in the premenstrual period. Maintaining a higher blood level of hormone by injections after the pain began was without benefit. Pregnenolone was given until the bleeding occurred. Menstruation, therefore, started during treatment rather than after withdrawal.

The pain of functional dysmenorrhea is probably not caused by uterine contractions. A more likely explanation would be secretory or

vascular congestion, possibly with muscular tetany, causing a pressure or ache with normal uterine contractions making the pain cramplike in character at times. Relief is usually obtained when patients begin to menstruate freely and some of the endometrium has sloughed off. As dysmenorrhea frequently begins a day or two before menstruation, it could not be caused by obstruction or clots. The abnormal sensation comes from the uterus as it can be stopped by cutting the nerves from this organ. What causes the condition is unknown. Glandular function is normal in many cases as near as it is possible to tell with present methods of diagnosis. However, there is no doubt that large doses of estrogens inhibiting ovulation, testosterone, or pregnenolone change the pain-producing mechanism in such a way as frequently to prevent the pain. They produce changes in the endometrium and changes in vasoconstriction. Of these three, pregnenolone seems preferable, as the use of the other two is nonphysiologic.

Occasionally, other physiologic endocrine therapy is indicated. Hypothyroid patients respond to thyroid therapy. The underweight patient is improved with a diet and insulin. The small undeveloped uterus with hypoplastic endometrium improves with small or moderate doses of estrogens. This study, however, was limited to the effect of products causing progestational changes and did not include cases treated with other endocrine preparations.

Summary

Eighty-two patients with functional dysmenorrhea were treated by giving pregnenolone orally. There was satisfactory improvement (50 per cent or better) in sixty patients. It was interesting to note that the small 5 mg. dose was effective. Nausea and vomiting did not occur when the pain was prevented. The improvement was limited mainly to the month treated. There was a tendency for the treatment to cause earlier menstruation. This method of treatment had many advantages, such as simplicity, harmlessness, and low cost. There was an important saving in the time of both patient and physician. In order for the treatment to be successful, it had to be given daily for seven to ten days before menstruation. When it was administered during menstruation, there was little benefit.

References

1. Bickers, W.: *AM. J. OBST. & GYNEC.* 43: 663, 1942.
2. Hartman, C. G.: *West. J. Surg.* 52: 139, 1944.
3. Greenblatt, R. B., McCall, E., and Torpin, R.: *AM. J. OBST. & GYNEC.* 42: 50, 1941.
4. Hamblen, E. C., Powell, N. B., Cuyler, W. K., and Pattee, C. J.: *Endocrinology* 26: 201, 1940.
5. Elden, C. A., and Wilson, K. M.: *AM. J. OBST. & GYNEC.* 32: 91, 1936.
6. Lackner, J. E., Krohn, L., and Soskin, S.: *AM. J. OBST. & GYNEC.* 34: 248, 1937.
7. Soule, S. D.: *J. Clin. Endocrinol.* 1: 567, 1941.
8. Winther, N.: *Lancet* 62: 428, 1942.
9. Sturgis, S. H., and Albright, F.: *Endocrinology* 26: 68, 1940.
10. Zondek, B.: *J. A. M. A.* 118: 705, 1942.
11. Henry, J. S., and Browne, J. S. L.: *AM. J. OBST. & GYNEC.* 45: 927, 1943.
12. Randall, J. H., and Odell, O. D.: *J. A. M. A.* 123: 735, 1943.
13. Wilson, L., and Kurzrok, R.: *Endocrinology* 27: 23, 1940.
14. Inhoffen, H. H., Longemann, W., and Serini, A.: *Ber. d. Deutsch. chem. Gesellsch.* 71: 1024, 1938.
15. Salmon, U. J., Walter, R. I., and Geist, S. H.: *Proc. Soc. Exper. Biol. & Med.* 40: 252, 1939.

16. Falls, F. H., Lackner, J. E., and Krohn, L.: J. A. M. A. 106: 271, 1936.
17. Macht, D. I.: Surg., Gynec. & Obst. 66: 732, 1938.
18. Campbell, R. E., and Hisaw, F. L.: AM. J. OBST. & GYNEC. 31: 508, 1936.
19. Shute, E. V.: Canad. M. A. J. 42: 145, 1940.
20. Novak, E.: South. M. J. 36: 145, 1943.
21. Sturgis, S. H., and Meigs, J. V.: Surg. Gynec. & Obst. 75: 87, 1942.
22. Fluhmann, C. F.: Endocrinology 23: 393, 1938.
23. Kotz, J., and Parker, E.: AM. J. OBST. & GYNEC. 37: 116, 1939.
24. Israel, S. L., and Mazer, C.: AM. J. OBST. & GYNEC. 36: 445, 1938.
25. Weinstein, B. B.: New Orleans M. & S. J. 96: 396, 1944.
26. Rutherford, R. N.: Clinics 2: 235, 1943.
27. Cinberg, B. L.: New York State J. Med. 42: 2138, 1942.
28. Bickers, W.: Virginia M. Monthly 69: 423, 1942.
29. Hirst, D. V., Hamblen, E. C., and Cuyler, W. K.: J. Clin. Endocrinol. 2: 442, 1942.
30. Boynton, R. E., and Winther, N.: J. A. M. A. 119: 122, 1942.
31. Hamblen, E. C.: J. Mt. Sinai Hosp. 8: 1200, 1942.
32. Branscomb, L.: J. M. A. Alabama 12: 81, 1942.
33. Gillman, J.: J. Clin. Endocrinol. 1: 331, 1941.
34. Frank, R. T., Goldberger, M. A., and Felshin, G.: Endocrinology 27: 381, 1940.
35. Geist, S. H., and Salmon, U. J.: N. Y. State J. Med. 41: 2220, 1941.
36. Inhoffen, H. H., and Hohlweg, W.: Naturwissenschaften 26: 96, 1938.
37. Hamblen, E. C., Cuyler, W. K., Pattee, C. J., and Axelsson, G. J.: J. Clin. Endocrinol. 1: 221, 1941.

947 WEST EIGHTH STREET

THE POSSIBLE ROLE OF BACTERIAL SYNERGISM IN PUERPERAL INFECTIONS DUE TO ANAEROBIC STREPTOCOCCI

SEYMOUR R. STEINHORN, B.S., M.S., CHICAGO, ILL.

(From the Department of Bacteriology, Northwestern University Medical School)

THE present report represents the results of an investigation of two points of interest concerning the role of anaerobic streptococci in puerperal infections. The first of these is the incidence of various bacteria in the uterus in infections following childbirth and abortion. Particular attention was directed to the relative frequency with which anaerobic streptococci are recovered as compared with hemolytic streptococci. Other studies of this aspect have yielded conflicting results. Secondly, what is the causal relationship of anaerobic streptococci to these infections? Investigation of this factor was deemed advisable since their role has been questioned on the basis of the absence of virulence for laboratory animals in previous experiments and their frequent occurrence in the vagina of normal women.

The association of anaerobic streptococci with puerperal infection has been recognized since the descriptions by Menge and Kroenig¹⁶ in 1899 and Natvig¹⁷ in 1905 of their presence in the lochia of women affected with this disease. Schottmüller²⁰ recovered them from the blood in similar cases. Schwarz and Dieckmann²¹ noted that these organisms were isolated from 64.3 per cent of their cases. In Colebrook's⁶ experience anaerobic streptococci alone or in association with other organisms caused two-thirds of the septicemias and one-third were due to hemolytic streptococci. Brown¹ reported the occurrence of anaerobic streptococci in 84.1 per cent of 246 cases. Somewhat different results were obtained by Harris and Brown⁹ who recovered anaerobic and hemolytic streptococci with almost equal frequency. Divergent observations were made by Fitzgibbon and Biggers⁸ who recovered hemolytic streptococci from 56 per cent of 51 patients and anaerobic streptococci from 2 per cent. In the experience of Rivett, et al.,¹⁰ there was a 39 per cent incidence of hemolytic streptococci while anaerobic streptococci occurred in 29.4 per cent of the cases.

The concept of bacterial synergism has been increasingly studied since Pasteur's¹⁸ observation that certain aerobes facilitated the growth of anaerobes by consuming the available oxygen. The term "bacterial synergism" was first employed, however, by Kümmerer¹¹ in 1923. Other investigations^{5, 10, 22, 23} indicate that this phenomenon occurs in many bacterial associations. The work of Meleney is closely related to the material of the present investigation. He¹³ showed that a nonhemolytic diphtheroid could augment the hemolysis of a double-zoned *Staphylococcus aureus*. Later he¹⁴ vividly demonstrated in vivo synergism with a microaerophilic nonhemolytic streptococcus and a faintly hemolytic *Staphylococcus aureus*. Meleney and his associates¹⁵ also reported similar results with other organisms. The postoperative synergistic gangrene of the abdominal wall which he described is frequently referred to as "Meleney's Gangrene."

The investigations of the pathogenicity of anaerobic streptococci have yielded almost uniformly negative results. Veillon²⁵ needed considerable amounts of his cultures to produce only subcutaneous abscesses in animals. Natvig¹⁷ and Schottmüller²⁰ failed to demonstrate any pathogenic activity. More latterly, McDonald, et al.,¹² were unable to produce lesions in animals by employing a variety of routes of injection of pure cultures of their twenty-three strains. They concluded that all their strains were practically nonvirulent for laboratory animals.

Materials and Methods

1. *Clinical Material*.—The 37 patients studied in this investigation were those with a temperature of 100.4° F., or above, which was sustained for twenty-four hours or more or occurred on separate occasions on two successive days within ten days of the birth or abortion. A clinical course satisfying these requirements was considered febrile. Most of the cases were diagnosed endometritis.

2. *Collection of Specimens*.—The vulva was carefully cleansed, a sterile speculum was inserted, and the orifice of the cervical canal was wiped with sterile gauze. Lochia was aspirated from the uterine cavity by means of a pipette made of a piece of glass tubing with a rubber bulb on one end. The pipette was in a large test tube, which was plugged with cotton and autoclaved as a unit prior to use.

3. *Media and Cultural Methods*.—Glucose infusion broth and thioglycollate broth² were used routinely for primary cultivation. Tubes of these were available at the bedside, and, immediately upon collection of the lochia, half of the total volume obtained was introduced into a tube of each of these media. This material was brought to the laboratory within two hours. Several loopfuls from the thioglycollate broth were streaked onto thioglycollate agar in the anaerobic dish described by Brewer.³ Material from the glucose broth was similarly plated onto two blood agar plates, one for aerobic, the other for anaerobic cultivation. These plates and the tubes inoculated at the bedside were incubated at 37° C. The aerobic blood agar plates and the glucose broth tubes were observed for growth at the end of twenty-four hours. Smears were made and any growth was subcultured on blood agar plates for pure culture study. Growth occurring in the thioglycollate broth was transferred to thioglycollate agar in the Brewer dish and to blood agar plates for anaerobic cultivation. The anaerobic jars were not opened before forty-eight hours of incubation. Any growth at the time of observation was transferred to thioglycollate agar in the Brewer dish and to two plates of blood agar for aerobic cultivation to determine the presence of facultative anaerobes or microaerophilic organisms.

4. *Pathogenicity of Anaerobic Streptococci*.—Pure cultures of anaerobic streptococci were transferred to blood agar plates and incubated anaerobically. These were observed daily for the first indication of growth, which usually required two to six days. At this time approximately one loopful of the surface growth was suspended in 3 c.c. of 0.85 per cent NaCl and mixed thoroughly. One cubic centimeter of this suspension was injected subcutaneously beneath the abdominal skin of each of three white mice. The animals were observed daily for evidence of infection. These tests were used as controls for the tests of synergism.

5. *Tests of Synergism in Vivo*.—The same suspensions employed in determining the pathogenicity of the anaerobic streptococci were used. Doses of 0.5 c.c. of these suspensions combined with 0.1 c.c. of suspensions of *Staphylococcus albus* (SAL-4), similarly prepared, were injected beneath the abdominal skin of each of three white mice of approximately equal size. Two additional mice were used as controls for the staphylococcus and were injected by the same route with 0.5 c.c. of the same suspension of staphylococcus alone. SAL-4 is the strain of *Staphylococcus albus* isolated from one case. Strains of staphylococci from all other

cases were tested in the same manner, as were three other strains isolated, respectively, from the normal human skin, from the normal human throat and from the air of the laboratory.

6. *Tests of Synergism in Vitro*.—Blood agar plates were streaked with parallel rows of anaerobic streptococci separated by a space about 1 cm. wide. Midway between two adjacent streaks a streak of a staphylococcus culture was made. The plates were incubated anaerobically and were observed daily for the appearance of growth.

Results

The percentage incidence of the various organisms is given in Table I. The predominating species were anaerobic streptococcus, hemolytic streptococcus, *Staphylococcus albus*, and *Bacterium coli*. Pure cultures of anaerobic streptococci were found in fourteen cases (37.8 per cent). The over-all occurrence of anaerobic streptococci both in pure culture and with other organisms was 45.9 per cent. Pure cultures of hemolytic streptococci were isolated from three cases (8.1 per cent) and in association with other organisms from four cases (10.8 per cent). In all, hemolytic streptococci were present in 18.9 per cent of all cases. *Staphylococcus albus* was recovered in pure culture and with other organisms in 29.7 per cent of the cases. *Bacterium coli* was identified in pure and mixed culture in 21.6 per cent of the cases.

None of the strains of anaerobic streptococci could be grown in the presence of oxygen even after long periods of artificial cultivation. Most of them, moreover, became nonviable after several months and none survived more than fourteen months.

TABLE I. THE INCIDENCE OF VARIOUS ORGANISMS IN THIRTY-SEVEN CASES OF PUERPERAL INFECTION

ORGANISM	NUMBER OF CASES	PERCENTAGE OCCURRENCE
Anaerobic streptococci alone	14	37.8
Anaerobic streptococci and others	3	8.1
Hemolytic streptococci alone	3	8.1
Hemolytic streptococci and others	4	10.8
<i>Staphylococcus albus</i> alone	4	10.8
<i>Staphylococcus albus</i> and others	7	18.9
<i>Bacterium coli</i> alone	3	8.1
<i>Bacterium coli</i> and others	5	13.5
<i>Streptococcus viridans</i> and others	2	5.4
<i>Hemophilus ducreyi</i> (?) and others	1	2.7
<i>Streptococcus anhemolyticus</i> and others	1	2.7
Diphtheroids	4	10.8

TABLE II. PATHOGENICITY AND BLOOD PLATE HEMOLYSIS RESULTING FROM THE ASSOCIATION OF SEVENTEEN STRAINS OF ANAEROBIC STREPTOCOCCI WITH A STRAIN OF STAPHYLOCOCCUS ALBUS (SAL-4)

STRAIN NUMBER	ACTION ON BLOOD AGAR	MICE WITH BOTH ORGANISMS			CONTROLS PURE CULTURES OF ANAEROBIC STREPTOCOCCI			CONTROLS PURE CULTURES OF STAPH. ALBUS (SAL-4)	
1	beta	+++	+++ 19	+++	0	0	0	0	0
3	beta	++	++	+++	0	0	0	0	0
4	beta	++	++	++	0	0	0	?	?
6	gamma	+	+	++	0	0	0	0	0
8	gamma	+	++	+	0	0	0	0	0
15	beta	+++	+++	+	0	0	0	0	0
16	beta	+++	+++ 17	+++ 15	0	0	0	?	0
17	beta	++	++	+++	0	0	0	0	0
18	beta	+++	++	+++	0	0	0	0	0
21	gamma	++	++	++	0	0	0	?	?
22	beta	+++ 7	+++	+++ 18	0	?	?	0	0
23	beta	+++	++	++	0	0	0	0	0
25	beta	+++	++	+	0	0	0	0	0
32	gamma	++	+++ 15	++	0	0	0	0	0
33	gamma	+	+	+	0	0	0	0	0
34	beta	++	+	+	0	0	0	0	0
37	beta	++	++	+++	0	0	0	0	0

? = slight reaction—swelling and erythema.

Numbers refer to days on which mice died after injection.

+ signs = relative degree of ulceration and necrosis.

The most striking results were obtained in observing the potentiating power of a strain of nonhemolytic *Staphylococcus albus* (SAL-4) on the hemolytic abilities and pathogenicity of the anaerobic streptococci (Table II). Whereas only one strain (5.9 per cent) was originally found to exhibit any hemolysis, and this was slight, twelve strains (70.5 per cent) manifested true beta hemolysis when grown in association with this strain of staphylococcus. The staphylococcus (SAL-4), when growing with the anaerobic streptococci, at times produced some hemolysis itself, but when this occurred it was slight.

Of even more direct interest were the results obtained in studying the in vivo effect of the staphylococcus (SAL-4) on the anaerobic streptococci. Pure cultures of anaerobic streptococci injected subcutaneously beneath the abdominal skin of mice produced a lesion in only one of seventeen cases and this was only a little swelling. Suspensions of the staphylococcus (SAL-4) produced only a slightly raised erythematous area in five mice which completely resolved in three to five days. When, however, one-half the amount of the same suspensions of anaerobic streptococci was mixed with one-fifth the amount of the suspension of the staphylococcus (SAL-4) and injected subcutaneously, marked ulceration and necrosis of the abdominal wall resulted, and in six instances the animals died (Table II). All other strains of *Staphylococcus albus* gave negative results, that is, no synergism could be detected either in vitro or in vivo.

Discussion

The occurrence of anaerobic streptococci in the majority of postpartum and postabortal infections as observed by others^{4, 6, 21} was reaffirmed in this investigation.

The contradictory results of other series may be explained by careful analysis of these reports. The citations by Fitzgibbon and Bigger⁸ of a 56 per cent incidence of hemolytic streptococci and that of Rivett, et al.,¹⁹ of a 39 per cent incidence of hemolytic streptococci and a 29.4 per cent incidence of anaerobic streptococci convey the impression that most of these infections are due to hemolytic streptococci. Furthermore, certain present-day textbooks of obstetrics give the same information. Actually, the figures of the studies referred to do not represent the averages of all cases but, rather, of the severely ill. It is generally conceded that most of the fulminating and fatal infections are caused by hemolytic streptococci, but that the majority of all cases of puerperal infection is due to these organisms is not supported by the available evidence. This is important because, while the sulfonamides have a definite therapeutic value in combating hemolytic streptococcal infections, they are practically useless against anaerobic streptococci, and any toxic drug manifestations may be detrimental to the recovery of patients infected with the latter organisms.

A discussion of the significance of anaerobic streptococci in puerperal infections recalls the correspondence of Armstrong and Burt-White² and Colebrook.⁷ The former questioned Colebrook's interpretations of his studies of puerperal infections and asked: "May it not be that the provocative factor is intrauterine manipulation, or trauma, and that the infection by various endogenous streptococci and other organisms is a sequel?" To this Colebrook answered: "Since I have seen seven women die from these infections and as many more in grave danger, during the past two years, I am inclined to attach considerable importance to them." It is true that these organisms are a part of the normal vaginal flora in a large number of women^{24, 26} but, nevertheless, their frequent presence in the infected uterus in pure culture indicates that they may participate in the actual invasion of tissue instead of being mere saprophytes. The aciduric bacilli are almost universal in their occurrence in the normal vagina, yet, they are conspicuous by their absence from the genital

tract of puerperal women. This indicates that while these bacilli are simple saprophytes and are unable to meet the defenses of the host, whether this be a specific bactericidal one or a pH shift, the anaerobic streptococci manifest some degree of invasiveness or, at least, a greater resistance than the vaginal bacilli. It is possible that the failure to demonstrate this invasiveness with pure cultures in experimental animals is due to species resistance and that, if a susceptible animal were found, this property might be elicited.

The results of the present study have elucidated, to some extent, the problem of the virulence of the anaerobic streptococci. It has been shown that, in association with a particular strain of a staphylococcus, these organisms may display marked virulence for mice and extensive hemolysis of blood agar, whereas either organism alone was incapable of producing these changes. The patient from whom this strain of staphylococcus was isolated also harbored an anaerobic streptococcus. The clinical course in this case was extremely stormy and ended fatally, the only death in the group. On the basis of the enhanced growth on the artificial media and the assumption of hemolytic activities, the anaerobic streptococci seemed to have derived all the benefit from the association; the staphylococcus never appeared to gain anything from the in vitro relationship.

In addition to the in vitro action of bacterial association, Meleney¹⁴ demonstrated that a strain of nonhemolytic microaerophilic streptococcus and a faintly hemolytic *Staphylococcus aureus* from a case of progressive gangrene of the abdominal wall produced gangrene in the skin of dogs and guinea pigs, when injected in amounts half as large as those of pure cultures which failed to evoke the lesion. The experimental results of the present study are in close accord with those of Meleney and his associates. The significance of the finding that such a synergistic process may be at work in certain cases of puerperal infection with anaerobic streptococci may have far-reaching implications. It has been shown that the type of organisms which many years ago was thought to be avirulent by numerous workers and more latterly by McDonald, et al.,¹² may, in fact, attain considerable virulence in infectious processes when associated with other organisms. The strain of staphylococcus used in this study was found purely by chance. This, nevertheless, illustrates the possibility that other potentiating strains, of other organisms as well, may exist.

In severe infections where an anaerobic streptococcus is recovered in pure culture, it is possible that initially another organism, the synergist, was also present but that it has been removed from the field by the defenses of the host, due, possibly, to a greater susceptibility of the synergist. It is also possible that in some instances the anaerobic streptococcus alone may be the cause of a serious postpartum infection. This may be explained on the basis of a lowered resistance of the patient or to some enhancement of the virulence of the organism by means other than synergistic.

In the past, but fleeting mention was made of "symbiosis" and related processes in connection with puerperal infections. With the demonstration that such a phenomenon actually occurs with these organisms in mice, further attention could profitably be focused along these lines of investigation.

Summary

1. The virulence of anaerobic streptococci is markedly potentiated by their association with a strain of *Staphylococcus albus* so that such mixtures are highly invasive for white mice.

2. Anaerobic streptococci represent the majority of bacteria isolated from the uteri of thirty-seven women with puerperal infection.

3. It is suggested that bacterial synergism may account for some cases of severe puerperal infection with anaerobic streptococci.

The author wishes to acknowledge the privileges accorded him by the Obstetrical Staff of Cook County Hospital.

References

1. Armstrong, R. R., and Burt-White, H.: Brit. M. J. 2: 305, 1930.
2. Brewer, J. H.: J. Bact. 39: 10, 1940.
3. Brewer, J. H.: Science 95: 587, 1942.
4. Brown, T. K.: Am. J. Surg. 48: 164, 1940.
5. Castellani, A.: J. A. M. A. 87: 15, 1926.
6. Colebrook, L.: Brit. M. J. 2: 134, 1930.
7. Colebrook, L.: Brit. M. J. 2: 446, 1930.
8. Fitzgibbon, G., and Bigger, J. W.: J. Obst. & Gynaec. Brit. Emp. 32: 298, 1925.
9. Harris, J. W., and Brown, J. H.: Bull. Johns Hopkins Hosp. 44: 1, 1929.
10. Holman, W. L., and Meekison, D. W.: J. Infect. Dis. 39: 145, 1926.
11. Kämmerer, H.: Klin. Wchnschr. 2: 1153, 1923.
12. McDonald, J. R., Henthorne, J. C., and Thompson, L.: Arch. Path. 23: 230, 1937.
13. Meleney, F. L.: Proc. Soc. Exper. Biol. & Med. 26: 205, 1928.
14. Meleney, F. L.: Ann. Surg. 94: 961, 1931.
15. Meleney, F. L., Olpp, J., Harvey, H. D., and Zaytseff-Jern, H.: Arch. Surg. 25: 709, 1932.
16. Menge and Kroenig: Monatschr. f. Geburtsh. u. Gynäk. 9: 703, 1899.
17. Natvig, H.: Arch. f. Gynäk. 76: 701, 1905.
18. Pasteur, L.: Compt. rend. Acad. d. sc. 52: 344, 1861.
19. Rivett, L. C., Williams, L., Colebrook, L., and Fry, R. M.: Proc. Roy. Soc. Med. 26: 1161, 1933.
20. Schottmüller, H.: Mitt. a. d. Grenzgeb. d. Med. u. Chir. 21: 450, 1910.
21. Schwarz, O. H., and Dieckmann, W. J.: South. M. J. 19: 470, 1926.
22. Sears, H. J., and Putnam, J. J.: J. Infect. Dis. 32: 270, 1923.
23. Sherman, J. M., and Shaw, R. H.: J. Gen. Physiol. 3: 657, 1920.
24. Soule, S. D., and Brown, T. K.: AM. J. OBST. & GYNEC. 23: 532, 1932.
25. Veillon, M. A.: Compt. rend. Soc. de biol. 45: 807, 1893.
26. White, E.: J. Obst. & Gynaec. Brit. Emp. 40: 630, 1933.

303 EAST CHICAGO AVENUE

EXPERIENCE WITH CONTINUOUS CAUDAL ANALGESIA IN OBSTETRICS AT THE UNIVERSITY OF MICHIGAN HOSPITAL

Report of 250 Consecutive Cases

GEORGE J. ANDROS, M.D., AND CHARLES W. HENDERSON, M.D.,
ANN ARBOR, MICH.

(From the Department of Obstetrics and Gynecology, University of Michigan Hospital)

CONTINUOUS caudal analgesia is being used at the University of Michigan Maternity Hospital for relief of pain during labor and delivery. At this time it is the procedure of choice in properly selected patients who do not present contraindications.

This preliminary report summarizes the results in the first 250 consecutive cases delivered via the vaginal route in which the caudal procedure was used. It does not include cesarean sections or gynecologic surgical cases where this form of anesthesia was employed. The 250 cases represent 79.7 per cent of all patients delivered vaginally during the period of time covered by this report.

The technique used is that of Hingson and Edwards, first described in 1942.¹ A malleable steel needle is inserted into the sacral canal through the caudal hiatus, and intermittent injections of 1.5 per cent Metycaine in Ringer's solution are carried out by means of a closed system incorporating a feeding syringe and a receptacle for the anesthetic agent.

The anesthetic agent acts extradurally in the sacral canal to obliterate motor and sensory impulses to and from the perineum and lower vagina (pudendal nerves), cervix and upper vagina (sacral parasympathetic fibers). Anesthesia and muscular relaxation of these structures are accomplished.

With injection of adequate amounts into the sacral canal, the height of the fluid agent in the posterior and lateral peridural space and the subsequent analgesic effect can be raised to the eleventh and twelfth thoracic segments—where thoracolumbar sympathetic fibers bearing pain impulses from the contracting uterine muscle enter the cord with the dorsal nerve roots.

Motor stimuli to the effective contractile elements of the uterus leave the spinal cord via sympathetic fibers at various levels higher than the tenth thoracic segment. Accordingly, it is possible to avoid inhibition of these impulses and diminution of uterine contractions by regulating the height of the effect through limitation of the volume of the injected agent.

The principal contraindications to continuous caudal analgesia include gross deformities or disease of the spine, sacrum, and central nervous system, fat pads obliterating the sacral hiatus, local infection at or near the site of needle insertion—including pilonidal cysts, psychic and emotional disturbances, a history of sensitivity to the drug. The procedure is withheld in the presence of such obstetric complications as placenta previa, abruptio placentae, severe cephalopelvic disproportion, floating head in a primiparous patient, predetermined monstrous and dead babies.

Results

In the present series, complete success was attained in 203 cases (81.2 per cent). This implies that labor was painless during the time caudal analgesia was used, and delivery was accomplished without discomfort to the patient and without recourse to supplemental anesthetic agent.

Listed as partially successful are 29 cases (11.6 per cent). In this group successful caudal analgesia during labor was deliberately terminated in 14 patients (5.6 per cent). In seven of these cases labor did not progress satisfactorily due to causes other than caudal analgesia, and it was deemed advisable to give the patient a complete rest. The caudal technique was discontinued and sufficient sedation to create a complete rest from labor was administered. In four other patients the analgesia was begun before labor had become well established, and the needle was removed after a period of lack of progress in the presence of ineffective uterine contractions. Emotional disturbance amounting to hysteria was the reason for terminating the caudal analgesia in two cases, and in one patient the needle was removed under the mistaken impression that a subsequent injection of the anesthetic agent had been made directly into the sacral plexus. Caudal analgesia was not restarted in any of these patients, and delivery was carried out with the aid of gas anesthesia.

Fifteen patients (6 per cent) on whom caudal analgesia was attempted obtained incomplete relief from pain or analgesia that could not be

maintained as long as necessary. Five patients in this group never were completely relieved of all discomfort, and four others became refractory to subsequent injections after a period of successful analgesia. In four cases the needle became dislodged toward the end of labor, and in two others the needle became plugged. It was necessary to deliver this group of patients with supplementary gas or open-drop ether anesthesia.

Complete failure occurred in 18 of 250 attempts (7.2 per cent). Two of these failures were due to introduction of the needle into an abnormally low-lying dural sac, resulting in the withdrawal of spinal fluid. No attempt to continue was made in these cases for fear of producing massive spinal anesthesia. Five patients were found to have congenital abnormalities of the sacrum, unrecognized before attempted insertion of the needle and incompatible with use of the caudal technique.

The remaining eleven failures were attributed to improper insertion of the needle. The subcutaneous tissue overlying the sacrum was the common site of misplacement. In no instance was a needle passed into the rectum. Most of the patients in this group were so obese over the sacrum as to make adequate palpation of the caudal hiatus difficult or impossible—in general, poor candidates for the procedure. Attempts at insertion of the needle in five of these cases were made during the terminal stages of labor in the presence of perineal bulging or crowning of the fetal head, which in itself constitutes one of the relative contraindications to the caudal technique. Postpartum roentgen studies in this group may have uncovered more abnormal sacra, since the incidence of congenital abnormalities of this bone incompatible with the caudal analgesia technique is greater than 5 per cent in females.²

As might be expected with increase in experience, there were less failures and unsatisfactory results in the last half of the series than in the first half.

Possible serious complications of the technique include inadvertent massive spinal anesthesia, intravenous injection (or rapid absorption through traumatized vessels) with subsequent vasomotor collapse or convulsions, infection of soft tissues, bone, or in the peridural space, and broken needles. (The latter complication is rare when the newer malleable steel needle and care are used.)

Postanalgesic neurological sequelae have been publicized among the laity, but in actual fact only one case of definite nerve damage subsequent to the caudal technique has been mentioned in the literature. Gready³ reported a personal communication from Hawkins describing in the latter's private practice a case of postpartum saddle anesthesia and disturbance of sensation and motor function in the right leg. Such a lesion may be due in part to damage of nerve roots beyond the reach of the caudal needle and cannot be assumed to be due to mechanical trauma. At the time of Gready's report spontaneous regression in signs and symptoms was taking place, and prognosis for ultimate recovery was believed good.

Increased incidence of urinary retention postpartum has not been noted in this series or in others where physiologic or isotonic solutions have been used as vehicles, and distention of the bladder during labor has been prevented by periodic catheterization. It is our technique to use an inlying catheter which is drained at least every hour that it is in place.

In this series there was no maternal mortality from any cause and no morbidity requiring additional hospitalization that could in any way be attributed to the caudal analgesia technique. No spinal anesthesia was produced and no needles were broken.

Infection was limited to one case of superficial cellulitis that responded rapidly to cruciate incision and drainage, and to a case of gluteal bursitis in an obese patient who received a subcutaneous injection of the drug. The bursitis responded well to local heat.

One patient demonstrated generalized clonic convulsive movements lasting a few seconds, along with syncope, nausea, and vomiting. This was attributed to rapid absorption of the metyrcaine through an area of traumatized blood vessels. The patient recovered within a few minutes without untoward effects, and the delivery of a normal baby proceeded uneventfully under unsupplemented caudal analgesia. Five other patients demonstrated less severe toxic reactions, consisting of vertigo, tinnitus, and momentary syncope. Induction of analgesia is preceded routinely by administration of 0.1 to 0.2 Gm. sodium pentobarbital (nembutal), which increases the patient's tolerance to the anesthetic agent and serves to mitigate possible toxic reactions.

Blood pressure drop of significant magnitude—due to vasodilatation in viscera and lower extremities from lumbar sympathetic block—is a common occurrence and must be watched for by frequent manometer checks after each injection. Prompt administration of vasopressor agents or autotransfusion by elevation of the legs generally corrects the hypotensive condition.

One hundred and twenty-seven cases (54.7 per cent) of the 232 who actually received caudal analgesia exhibited a systolic blood pressure fall of greater than 20 mm. Hg, but all patients responded quickly to the treatment mentioned above, and no embarrassment of fetal circulation or untoward reaction in the mother was recorded.

Nine intrapartum and postpartum fetal deaths were recorded among the 250 deliveries in this series, giving a gross uncorrected fetal mortality rate of 3.6 per cent. When corrected for unavoidable deaths the fetal mortality rate is seen to be 2 per cent. None of the fetal deaths could in any way be attributed to the use of caudal analgesia.

TABLE I. SUMMARY OF FETAL DEATHS

DESCRIPTION OF FETUS	NUMBER OF CASES
(a) Previa ble Fetus (Weight less than University of Michigan minimum standard of 1,000 Gm.)	2
(1) 345 Gm.	
(2) 435 Gm.	
(b) Term fetus with abnormality incompatible with life confirmed by autopsy findings	2
(1) Congenital absence of diaphragm	
(2) Von Gierke's disease	
(c) Premature fetus (Weight less than 2,500 Gm.)	3
(1) 1,005 Gm.	
(2) 1,710 Gm.	
(3) 1,860 Gm.	
(d) Term or near-term fetus dying in the immediate postpartum period from overwhelming infection	2
(1) Bilateral confluent pneumonia	
(2) Multiple abscesses	

It has been noted by others and supported by our observations that one of the most striking, and certainly most significant, phenomena occurring in labor and delivery under continuous caudal analgesia is the rapidity with which the infant breathes and cries lustily after the head is born. The vital mechanisms of the fetus are not obtunded by narcotics or general anesthetic agents that might otherwise be used. Trauma to the fetal head likewise is minimized in the presence of relaxed and softened musculofascial pelvic structures and with the absence of violent expulsive efforts on the part of the mother. These factors make continuous caudal analgesia highly desirable in premature labor, where the underdeveloped fetal structures are particularly delicate.

Because the parturient loses the urge to bear down, it was feared early in the development of caudal analgesia that operative interference

for delivery would be increased to such an extent as to constitute a definite hazard to mother and fetus. With proper management of labor and delivery, major operative interference need not be increased. In 200 cephalic presentations in this series where actual delivery took place under unsupplemented caudal analgesia, forceps were used in 154, or 77 per cent, of the cases. This compares with 20.7 per cent forceps deliveries in this clinic during the whole year of 1942—before any caudal analgesia was used.

While operative interference in our series rose from 20.7 per cent to 77 per cent, this increase loses much of its significance when it is noted that no "high" or "midforceps" were necessary in the caudal series. Sixty-three of the 154 forceps deliveries in this group were classified as "low forceps" and the other 91 were of the "outlet" variety, consisting of "lifting" the presenting head through the introitus after perineal bulging or crowning of the fetal scalp had occurred.

Failure of complete and spontaneous rotation of the head due to loss of tone and resistance in the musculofascial sling of the birth canal has been mentioned as a drawback of caudal analgesia and a potential source of traumatic operative interference. In the 154 cephalic cases terminated by forceps delivery, only 19 failed to show spontaneous rotation of the presenting part (occiput in all cases) into one of the anterior quadrants of the pelvic outlet. This amounts to 9.5 per cent of all cephalic cases actually delivered under caudal analgesia alone. The incidence of failure of spontaneous rotation in cephalic presentations in this clinic was 3.6 per cent in 1942.

In six of these 19 cases of failure of rotation beyond the transverse position, manual rotation preceded forceps delivery, and in 12 others forceps rotation was carried out. One infant was delivered as a persistent occiput posterior. It should be emphasized that all of these operative procedures were carried out with the head low in the pelvis and were simplified and made less traumatic than under inhalation anesthesia because of the relaxation of pelvic soft tissue structures produced by the caudal technique.

Our observations on length of labor under continuous caudal analgesia support the findings of Hingson and Edwards.⁴ The average duration of labor as a whole, and of the first stage (stage of cervical dilatation) in particular, is shorter than with other forms of analgesia. Only when the presenting part is allowed to rest neglected on the perineal floor need the second stage of labor be significantly increased in duration. The average multipara, alert and cooperative under this form of analgesia, can generally expel the fetal head over the perineum by the voluntary fixation of the diaphragm and contraction of abdominal muscles, when informed of the occurrence of a (painless) uterine contraction by the attending accoucheur. The uninitiated primiparous individual does not coordinate so well her efforts, but, with little or no effort on her part, the presenting part generally is brought to the perineum and can be "lifted" gently through the introitus by "outlet" forceps.

The third stage of labor likewise is shortened under continuous caudal analgesia. The absence of inhibition of the contractile elements of the uterus decreases the period of postdelivery uterine relaxation or atony, and third-stage blood loss is diminished in most cases. Average estimated

blood loss in those cases in this series delivered under unsupplemented caudal analgesia was less than 150 c.c. In 500 cases Lull⁵ found an average blood loss of 111 c.c. These figures compare favorably with average blood loss during labor (about 300 c.c., DeLee) with other forms of analgesia and anesthesia. Much of the blood loss under caudal analgesia comes from dilated vessels cut during episiotomy, and can be controlled by hemostatic clamping and ligation of the larger vessels and by sponge pressure on the cut surfaces.

Since the effectiveness of continuous caudal analgesia tends to decrease as its duration in any given patient is prolonged (refractory response to subsequent injections tends to increase progressively after 8 to 10 hours), it is our policy to delay the induction of analgesia until labor is well established and the patient is experiencing pain and not mere discomfort. In primiparous patients the introduction of the needle is not made until the cervix is well effaced and dilated at least 3 to 4 cm., and the head is well engaged in the pelvis. In multiparas the analgesia is induced as soon as significant progress is noted. This obviates the need of haste in the late stages.

Duration of successful analgesia in this series ranged from twenty minutes to twenty-two hours. The average length of time was two hours and thirty-six minutes in multiparas and five hours and forty minutes in primiparas.

Approximately 0.36 Gm. of metycaine is used every hour, calculated on the basis of a 30 c.c. initial injection of the 1.5 per cent solution and the requirement in the average case of a subsequent dose of 20 c.c. every fifty minutes.

We have mentioned the value of experience in attaining good results with continuous caudal analgesia. Careful attention to the patient is an equally important prerequisite to success and complete safety. All of the cases in this series have been managed by three properly trained members of the instructor and resident staff. The responsibility of the anesthetist-obstetrician in each case does not end with the insertion of the needle, but, rather, the patient is followed closely through labor and delivery. Subsequent injections of the anesthetic agent are given by the attending staff physician in each case and the effects evaluated by him. Any aberration from the usually expected results are noted and corrective procedures carried out as necessary. Turning the patient from side to side during labor, transporting her to the delivery room and placing her properly upon her back are carried out under the direct supervision of the physician. Blood pressure readings are taken at ten- to fifteen-minute intervals after each injection and after the patient has been placed upon her back for delivery. Therapeutic measures for fall in blood pressure are instituted promptly.

In any consideration of the advantages and difficulties of continuous caudal analgesia, certain more or less intangible factors not suitable for statistical evaluation should be mentioned. Older obstetricians familiar with the discomfort associated with labor during precaudal days cannot help but be impressed, and relieved, by the well-being of patients in labor under continuous caudal analgesia. The parturient remains at ease mentally as well as physically. Fear and anxiety are absent. Emotional tension is minimal, and the restlessness and irrational

eries so often associated with use of amnesic and analgesic drugs do not cloud the picture of labor for the patient and her attendants. The fully conscious patient is able to take nourishment and adequate amounts of fluids during the course of labor. Reflex vomiting is infrequent. As the end of labor approaches, the patient may be moved into the delivery room without haste, and preparation of the patient can be quietly and adequately carried out. Delivery is performed with deliberation and care. Following delivery the mother may be able to eat and drink immediately, and postpartum convalescence appears to be hastened because the patient under continuous caudal analgesia suffers a minimum of mental and physical exhaustion.

Summary

In summary, certain characteristics of continuous caudal analgesia in obstetrics reported by others are further supported by our experience with 250 consecutive cases:

1. Complete relief of pain during labor and delivery may be obtained, without impairment of consciousness or abolishment of voluntary motion, and without interference of uterine contractions.

2. The respiratory and other vital mechanisms of the child are not depressed.

3. Labor is shortened in most cases.

4. Blood loss during labor is decreased, and postpartum hemorrhage is minimized.

5. The incidence of operative delivery is definitely increased, but consists chiefly of outlet forceps. There was no increase in any of the major or more serious obstetric operative procedures in our series.

References

1. Hingson, R. A., and Edwards, W. B.: *Am. J. Surg.* 57: 459, 1942.
2. Trotter, M., and Letterman, G. S.: *Surg., Gynec. & Obst.* 78: 419, 1944.
3. Gready, T. G.: *J. A. M. A.* 123: 671, 1943.
4. Hingson, R. A., and Edwards, W. B.: *J. A. M. A.* 123: 538, 1943.
5. Lull, C. B.: *AM. J. OBST. & GYNEC.* 47: 312, 1944.

CESAREAN SECTION UNDER FRACTIONAL SPINAL ANESTHESIA

WILLIAM LEVINE, M.D., F.A.C.S., BROOKLYN, N. Y.

(From the Department of Obstetrics and Gynecology at the Beth-El Hospital)

THE use of single dose spinal anesthesia in cesarean section has long been advocated by Cosgrove.¹ Although it is ideal for the operator because of the marked abdominal relaxation, diminution of blood loss and noninterference with initiation of respiration of the newborn infant, maternal deaths and near-deaths have been reported. Waters² reported one death in 3,000 cases and in addition refers to several close calls and near-deaths from the use of single dose spinal anesthesia. Plas and Ricci³ report three deaths from bulbar syncope despite careful selection of patients and extreme caution in its administration.

Beck,⁴ Gordon and Rosenthal,⁵ DeLee,⁶ Greenhill,⁷ and many others agree that proper selection of the anesthesia reflects a good result, but condemn spinal anesthesia because of its particular danger in pregnant women. Greenhill stresses sudden death as a great danger in spinal anesthesia and attributes it to respiratory paralysis. Although single dose spinal anesthesia proved satisfactory in our experience we abandoned its use because of the above and many other adverse reports.

The return to the use of general anesthesia has been very disappointing because of the many complications encountered, as will be shown later. Local infiltration was found to be time-consuming and did not always produce proper anesthesia. Some advocate supplementing it with general anesthesia, particularly at the time the fetus is removed and when the placenta is extracted. In 1942, Lemmon and Paschal⁸ reported 1,000 surgical cases including 62 cesarean sections, operated upon under continuous spinal anesthesia. A more recent report by Lemmon and Hager⁹ supplements the original report and summarizes their results in 2,000 surgical cases which include 140 cesarean operations.

This method has the advantage of administering a small amount of anesthetic solution and adding more if and when needed. They contend that all forms of anesthesia are administered fractionally as the patient requires it. For instance, inhalation anesthesia is continued in concentrations and for as long a time as the surgeon needs it to complete the operation. Similarly, in local anesthesia, more anesthetic fluid is added when the patient complains of pain. Even in intravenous anesthesia the amount given is as required, and not necessarily the entire dose empirically prescribed. An initial small dose of the drug with the spinal fluid can be withdrawn should unforeseen toxic symptoms appear, because the flexible needle remains in situ throughout the operation. The fractional administration of the drug has particularly appealed to us. The continuous feature which is of benefit in prolonged operations is not necessarily applicable in cesarean operations. Table I reveals the types of anesthesia in our last 286 cesarean operations. We wish to report mainly our results in the 144 operations done under fractional spinal anesthesia, and compare them with the results in the 103 operations performed under general anesthesia.

TABLE I. TYPES OF ANESTHESIA

Fractional spinal	144
General	103
Local infiltration	19
Caudal	14
Local and general	4
Unrecorded	2
Total	<hr/> 286

We have used 8 c.c. of spinal fluid to dissolve 200 mg. of procaine crystals. Each cubic centimeter of this solution therefore contains 25 mg. of procaine. The spinal canal is entered between the third and fourth or fourth and fifth lumbar interspace, with the patient lying in left lateral position. The connecting tube is then attached to the flexible spinal needle. The patient is then placed in the dorsal recumbent position and 2 c.c. (50 mg.) are injected slowly through a syringe connected at the opposite end of the tubing. This produces a closed sterile circuit and subsequent injections of 1 c.c. are given as needed, usually within thirty minutes after the first injection, and still further injections of 1 c.c. are given at fifteen-minute intervals.

The Trendelenburg posture is not needed. The natural curvature of the spine will cause the procaine solution to rise cephalad, sufficiently high to produce adequate anesthesia for operation. The level usually reached is about that covered by the eighth thoracic nerve.

Preoperative administration of ephedrine sulfate is rarely necessary, for the fall in blood pressure is minimal with a 50 mg. dose. If the blood pressure at the start of the operation is below 120 systolic, ephedrine sulfate, $\frac{3}{4}$ grain, is administered. Slight nausea is sometimes encountered, and this is combated by inhalation of a pungent medicament such as aromatic spirits of ammonia. Oxygen inhalation sometimes controls this nausea.

Venoclysis is rarely needed unless as a preliminary to a planned blood transfusion. Morphine sulfate, $\frac{1}{4}$ grain, is administered as soon as the baby is extracted and oxytocic drugs are administered soon after the placenta is removed. The patient remains relaxed, comfortable, and composed throughout the operation. When the patient complains of pain the additional dose of 25 mg. of procaine is conveniently added.

Fifty milligrams of the drug administered initially is generally sufficient for all the intra-abdominal work. The additional 25 mg. is given for closure, and only when necessary. Table II shows that in 8 instances the operation was completed with only 50 mg. of procaine. In 72 instances the operations were started with 50 mg. of the drug and were completed by adding 25 mg. more after thirty minutes. Forty-one cases required up to 100 mg. of the drug in divided doses. There were also 23 patients who required over 100 mg. of the drug for the completion of the operation. This does not imply that many operations consumed over one hour of operating time. In instances where more than 100 mg. of procaine were used, the patients had a special insensitivity to the drug, or they were obese and large, thus requiring more drug to produce suitable anesthesia.

TABLE II. AMOUNT OF DRUG USED

MG.	MG.	MG.	MG.
50	50-75	50-100	Over 100
8	72	41	23

Table III reveals that the operating time in 14 patients was over one hour, and in only 32 instances the operations lasted thirty minutes or less. There were 72 operations which lasted between thirty and forty-five minutes, and 26 operations lasted forty-five to sixty minutes. The average operating time was 44.5 minutes.

TABLE III. TIME OF OPERATION

30 MIN. OR LESS	30-45 MIN.	45-60 MIN.	MORE THAN 60 MIN.	AVERAGE TIME
32	72	26	14	44.5

There is a remarkable diminution in blood loss during the operation. The uterus after extraction of the baby and placenta is firm, hard, and pale instead of the usual soft, beefy red color of the gravid uterus. It remains so throughout the operation and the field is free from blood. Only 8 transfusions were needed in the series of 144 cesarean operations under fractional spinal anesthesia, and 5 of these were for replacement due to loss in antepartum bleeding. In the 103 patients operated upon under general anesthesia 18 transfusions were given. Eight of these were given for antepartum hemorrhage, and the remaining 10 for bleeding incident to loss of blood during the operation, as illustrated in Table IV.

TABLE IV. TRANSFUSIONS

	FRACTIONAL SPINAL	GENERAL
Antepartum bleeding	5	8
For blood loss at operation	3	10
Total	8	18

The postoperative course is unusually smooth. Food is tolerated much sooner after the operation. Distention is at a minimum and the postoperative recovery is unusually rapid. The average postoperative hospital stay was 11 days. The shortest stay in the hospital was 9 days, and the longest stay was 26 days. In the group of 103 patients that received general anesthesia, the postoperative stay was much longer. Here the average stay was 14 days, the longest stay was 58 days, and the shortest stay was 11 days.

TABLE V. RESULTS IN INHALATION ANESTHESIA SERIES

No Complications	85
Complications (Several had more than one complication)	15
Endometritis	5
Wound infection	4
Bronchopneumonia	3
Postoperative uterine bleeding	2
Acute gastric dilatation	1
Paralytic ileus	1
Thrombophlebitis and pulmonary infarction	1
Pyelitis	1
Trigonitis	1
Abdominovesical fistula	1
Deaths	3
Cardiovascular collapse	1
Peritonitis	2

The results from general anesthesia are listed in Table V. There were 85 patients who had no complications, and 15 patients had one or more of the complications listed. Some of these complications cannot be attributed to the form of anesthesia used. However, in the instances of bronchopneumonia, postoperative uterine bleeding, endometritis, acute gastric dilatation, and a few others, the anesthetic is directly the cause or has prepared a basis for the complication. The three maternal deaths in this group were not directly related to the anesthetic. They were not anesthetic deaths. One patient died of cardiovascular collapse. She was suffering from rheumatic heart disease and had decompensated on two occasions during her pregnancy. She was in the hospital for observation and treatment prior to operation, and was operated upon under novocain infiltration anesthesia supplemented by nitrous oxide and oxygen. She died twenty-four hours later of cardiovascular collapse. The other two patients died on the seventh and eighth postoperative days, of peritonitis.

Table VI indicates the results under fractional spinal anesthesia. There were 138 patients with no complications. Two had abdominovesical fistulas following the Waters' extraperitoneal operation; one had mastitis; one had an abdominal wound infection; and there was only one instance with marked abdominal distention which abated on the seventh postoperative day. In this group of 144 cases there was only one death, which cannot be attributed to the anesthesia. This patient died on the tenth postoperative day of uremia following the administration of Rh incompatible blood.

TABLE VI. RESULTS IN FRACTIONAL SPINAL SERIES

NO COM- PLICATIONS	COMPLICATIONS				DEATHS
	Abdomino- vesical Fistulas	Mastitis	Marked Intestinal Distention	Wound Infection	Uremia due to Rh incom- patibility
138	2	1	1	1	1

Summary

1. Fractional spinal anesthesia has been satisfactorily used in 144 cesarean operations.

2. An initial dose of 50 mg. of the drug did not produce toxic manifestations or cause severe drop in blood pressure, and was sufficient for all the major intraperitoneal work. Additional anesthetic was conveniently added as needed.

3. There was a minimal amount of bleeding and greater facility during the operation. The uterus remains well contracted during the operation and throughout the puerperium. There were no instances of early or late postoperative bleeding.

4. There were fewer transfusions given in this series in contrast with the number given in the series which were operated upon under general anesthesia.

5. The postoperative course was smoother, complications fewer, and hospital stay shorter.

6. There was one maternal death in this series, not in any way related to the anesthetic.

Appreciation is expressed to Dr. Jacob Herzlich for planning the technique and administering all fractional spinal anesthetics in this study.

References

1. Cosgrove, S. A., Hall, P. O., and Gleason, W. J.: *Current Researches in Anesth. & Analg.* 16: 234, 1937.
2. Waters, E. G.: *New England J. Med.* 226: 380, 1942.
3. Plas, P., and Ricci, G.: *Bu. Soc. de Obst. y Ginec. de Buenos Aires* 20: 817, 1941.
4. Beck, A. C.: *AM. J. OBST. & GYNEC.* 44: 558, 1942.
5. Gordon, Chas. A., and Rosenthal, A. H.: *Am. J. Surg.* 54: 528, 1941.
6. DeLee, J. B.: *The Principles and Practice of Obstetrics*, ed. 8, Philadelphia, 1943, W. B. Saunders Co., p. 287.
7. Greenhill, J. P.: *S. Clin. North America* 23: 143, 1943.
8. Lemmon, W. T., and Paschal, G. W., Jr.: *Surg., Gynec. & Obst.* 74: 948, 1942.
9. Lemmon, W. T., and Hager, H. G., Jr.: *Ann. Surg.* 120: 129, 1944.

THE CIRCULATION OF AMNIOTIC FLUID

WILLIAM F. MENGERT, M.D., AND J. W. BOURLAND, M.D.
DALLAS, TEXAS

(From the Department of Obstetrics and Gynecology of the Southwestern Medical College and the Dallas Medical and Surgical Clinic)

FOUR theories are current concerning the origin of amniotic fluid. According to these, it is: (1) derived from fetal urine, (2) a transudate from maternal blood, (3) secreted through the amniotic epithelium, (4) of mixed origin. Williams⁷ believes that, "from the evidence at present available, it would appear that under normal conditions the amniotic fluid is derived primarily from the maternal serum, which may be modified during its passage through the amniotic epithelium; but that under abnormal conditions other sources, more particularly the fetal urine, will have to be taken under consideration." This is the most generally accepted theory, except that many do not subscribe to the idea that fetal urine contributes significantly.

If amniotic fluid is derived from the maternal serum, it follows that there is probably continuous production, and unless hydramnios develops, continuous disposal. Taussig⁵ believes, "that normally there is an outflow as well as an inflow" of amniotic fluid. Polano⁴ and DeSnoo¹ concur, and these three authors believe that amniotic fluid normally is ingested by the fetus and eliminated by way of the fetal and maternal blood streams. DeSnoo believes that the principal, and practically the only, channel of elimination is by way of the fetal intestinal tract. Demonstration of lanugo hairs and epidermal cells in the fetal stomach and intestines at postmortem examination, and of epithelial cells in meconium of the living newborn infant,³ offers ample evidence for the ingestion of amniotic fluid during pregnancy. Other evidence concerning disposal mechanisms has been obtained by following the fate of dyes experimentally introduced into the amniotic cavity.

Since there seems to be little question concerning the continuous disposal of amniotic fluid, there must be some mechanism to regulate the amount produced in normal pregnancy. DeSnoo believes that the quantity swallowed by the fetus affects production. In other words, if intra-amniotic fluid pressure is low, there will be increased transudation from the maternal serum; if high, diminished transudation.

Normally, these regulatory mechanisms are adequate for the relatively minor variations in quantity of fluid swallowed by the fetus. On the other hand, in the presence of serious obstruction of the absorptive process, hydramnios could result. Massive interference with outflow might be expected to diminish production, but probably not to eliminate it altogether.

Obviously, congenital atresia of the fetal gastrointestinal tract would represent a massive blockade to the outflow of amniotic fluid. As a corollary, it might be postulated that such obstruction must be situated relatively high in the gut, since blockage of the large bowel, for example, would interfere with neither ingestion nor absorption.

It was, therefore, with considerable interest that each of the authors observed the development of hydramnios in a pregnant woman whose baby was born with a duodenal atresia. The following two case reports are presented because we believe that the gestational effects of the natural experiment resulting from the anomaly lend considerable support to the theory of continuous production and absorption of amniotic fluid during normal pregnancy.

CASE 1.—Mrs. G. N., Hospital No. G510,* a gravida iii, aged 36 years, with two living children, was first seen at the University of Iowa Hospitals, Sept. 16, 1937, at about the twentieth week of her fourth pregnancy, at which time nothing abnormal was noted. Eight weeks later it was noted that the uterus was unduly large, with the fundus higher than expectancy for the calculated duration of pregnancy. By the thirty-third week of gestation there was definite hydramnios. A fetus corresponding in size to the duration of pregnancy could be palpated, although the uterus was as large as, or larger than, a pregnancy at term. A roentgenogram of the abdomen revealed no evidence of fetal skeletal deformity.



Fig. 1.—The liver has been displaced to the right. The stomach and duodenum have been lifted up and to the left so that the posterior surfaces are visible. The "shaft" of what looks like a dumbbell is the distended pylorus. The transverse line across the distended portion of the duodenum is an artifact produced by traction on the superior hemostat.

The atretic portion of the gut lies immediately superior to the inferior hemostat, between it and the distended duodenum. The probe lies under the common duct.

Labor began prematurely at the thirty-sixth week, probably because of excessive uterine distention, and resulted in the spontaneous birth of an apparently normal male child weighing 2,750 grams. There were approximately 2,000 c.c. of amniotic fluid. The maternal puerperal course was uneventful.

*Permission to use this case report was kindly granted by Dr. E. D. Plass, Iowa City, Iowa.

The infant cried spontaneously and presented no evidence of abnormality. Fourteen hours after birth he regurgitated a small amount of a feeding, but had taken those before, and took some after, without difficulty. Regurgitation after feedings became the rule thirty-one hours after birth and increased both in frequency and in force until almost all of each feeding was returned with a projectile type of vomiting. Feeding by gavage was attended with a similar result. Small stools of meconium were passed. The infant's condition rapidly became worse, with cyanosis, apnea, and weak heartbeat, and death occurred 77½ hours after birth. An atresia of the duodenum, 5 cm. distal to the pylorus, was discovered at postmortem examination. The block was complete and permitted passage of neither a probe nor water. In addition, there was pulmonary congestion and edema which may have resulted from aspiration of regurgitated food. The report of the pathologist follows:

"The stomach was considerably distended, and the duodenum was widely distended to a point 5 cm. distal to the pylorus. Gas, and white semifluid material filled the stomach and the distended duodenum. The pylorus was distended and patent with walls of normal thickness. The duodenal lumen was completely closed just proximal to the entrance of the common duct as demonstrated by inability to pass a probe or fluid. Below the point of atresia the gut was quite small and contained only a very small amount of meconium."

"The common duct entered the duodenum 5 mm. distal to the atresia, and the duct of Wirsung joined the common duct 4 mm. from the ampulla of Vater. The remainder of the gastrointestinal tract, including the anus, was freely patent. The gall bladder contained a normal amount of bile. The rest of the body was essentially normal."

Anatomic Diagnosis.—Congenital atresia of the duodenum 5 cm. distal to the pylorus; pulmonary congestion and edema (Fig. 1).

CASE 2.—MRS. W. R. E.* was first seen Dec. 6, 1937, in the sixth week of pregnancy, at which time she weighed 115½ pounds. The pregnancy proceeded normally with questionable distention of the uterus until the twenty-seventh week, when it was noted that the uterus was markedly distended with fluid. By the thirty-first week there was definite hydramnios and the fetal heart tones could not be heard. During the thirty-sixth week the patient weighed 164 pounds (a gain of 48½ pounds) and was complaining of dyspnea. The membranes were ruptured artificially and the patient was delivered spontaneously of an apparently normal 2,841-gram female child after an escape of 4,600 c.c. of fluid. The maternal postpartum course was uneventful.

Regurgitation of food with strangling and cyanosis began on the second day of life, and the vomitus soon became bile stained. There was one small stool of meconium. A diagnosis of congenital obstruction of the duodenum was made and duodenojejunostomy performed by Dr. J. W. Duckett on the fourth postnatal day.

Operative Findings.—"The stomach and proximal portions of the duodenum were found to be greatly dilated and thick-walled. There was an abnormally high attachment of the mesentery of the ascending colon and cecum; and, apparently because of this attachment, there was a fold of peritoneum overlying the duodenum at its most posterior location producing some occlusion of the lumen. It is probable that the obstruction of the lumen was due mainly to an intrinsic defect such as persistent diaphragm. The jejunum and large intestine were normal in appearance wherever seen." A duodenojejunostomy, anastomosing the second portion of the duodenum with the proximal end of the jejunum, was performed. "When the duodenum was opened, a catheter was passed upward into the stomach, meeting no obstruction;

*Permission to use this case report was kindly granted by Dr. J. W. Duckett,² and the J. B. Lippincott Company, publishers of the *Annals of Surgery*.

and was then passed downward to the point of obstruction at the base of the mesocolon." (Fig. 2.)

Breast milk was fed during the postoperative course and was vomited only twice. Supportive treatment included the administration of CO_2 and O_2 and infusions of saline and dextrose. The child has been seen frequently since; her development has been entirely normal and she has enjoyed excellent health.

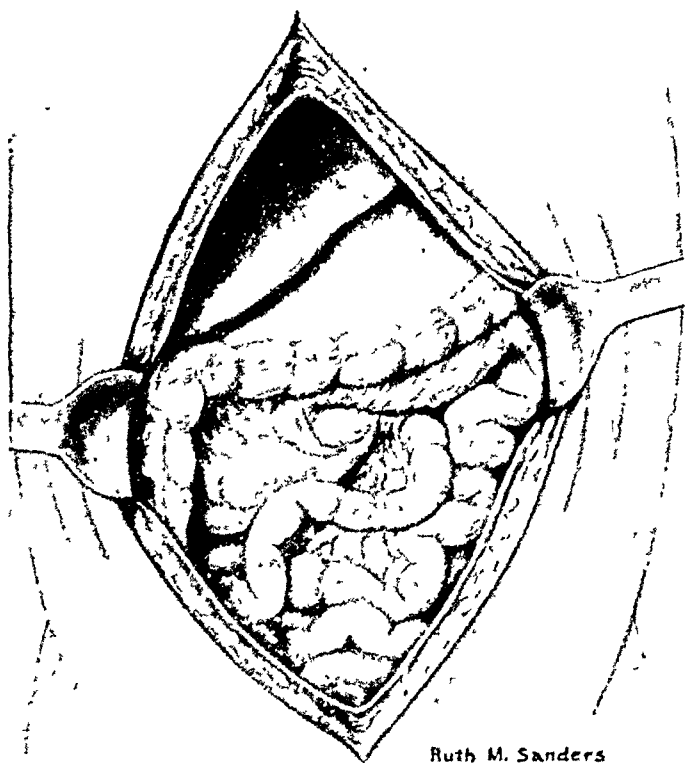


Fig. 2.—The atretic portion of the duodenum is seen just below the greater curvature of the stomach, the edge of which is visible below the transverse colon. The distended upper portion of the duodenum is seen beneath the angle formed by the ascending and the transverse colon. (Reproduced from the *Annals of Surgery*.)

Discussion

The case histories of these two children, with regard to the mothers' pregnancies, the symptoms during the first few days of life, and anatomic findings were strikingly similar. Each had an atresia of the duodenum. It seems reasonably safe to conclude that the maternal hydramnios resulted in each case from the inability of the fetus to ingest and absorb amniotic fluid. That fluid was swallowed is attested to by the remarkable distention of the stomach and proximal portion of the duodenum of each child. These two natural experiments give strong support to the theory that normally there is an outflow as well as an inflow of amniotic fluid.

On the other hand, the general belief that a large part of the fluid necessary for fetal development is obtained through ingestion of amniotic fluid is not sustained, since each of these children was normally developed at birth at the thirty-sixth week of gestation and weighed 2,750 and 2,841 grams, respectively. Since these weights are normal for infants born about the thirty-sixth week, it would seem that failure to absorb usual quantities of amniotic fluid did not interfere with general development.

From the clinical standpoint, it is likely that hydramnios developing during the second half of pregnancy, coupled with early and persistent postnatal regurgitation in an otherwise normal-appearing infant, should offer strong evidence of an intestinal atresia located near the stomach. Such infants should be operated upon without delay. On the other hand, hydramnios may be absent in atresias of the jejunum and below, since in such cases sufficient portions of gut remain available for absorption. Therefore, although this syndrome seems to be definitive for high duodenal atresia, absence of hydramnios does not exclude the possibility of intestinal block at a lower level. At the time of Webb and Wangenstein's⁶ report in 1931 on "Congenital Intestinal Atresia," there had been only nine reports of successful surgical attack upon this anomaly. Since then there has been a gratifying increase in the number of reports of infant salvage. Atresias of the intestine are fortunately rare and it is estimated⁶ that they occur with a frequency of about 1 in 20,000.

Summary and Conclusions

Present concepts of the origin and circulation of amniotic fluid are discussed. The anatomic findings in two infants with duodenal atresia, whose mothers developed hydramnios during the second semester, are presented to support the theory that there is a constant absorption as well as production of amniotic fluid during normal pregnancy.

Failure to absorb usual quantities of amniotic fluid did not influence the gestational development of these two infants.

The association of hydramnios with subsequent birth of a normal-appearing infant who speedily develops persistent and forceful vomiting appears to be a syndrome characteristic of atresia of the upper portion of the duodenum.

References

1. DeSnoo, K.: *Monatsschr. f. Geburtsh. u. Gynäk.* 105: 88, 1937.
2. Duckett, J. W.: *Ann. Surg.* 116: 321, 1942.
3. Farber, S.: *J. A. M. A.* 100: 1753, 1933.
4. Polano, O.: *Ber. ü. d. ges. Gynäk. u. Geburtsh.* 3: 1, 1924.
5. Taussig, Fred J.: *AM. J. OBST. & GYNEC.* 14: 505, 1927.
6. Webb, C. H., and Wangenstein, O. H.: *Am. J. Dis. Child.* 41: 262, 1931.
7. Stander, H. J.: *Williams Obstetrics*, New York and London, 1941, D. Appleton-Century Co., Inc.

VITAMIN E IN MENOPAUSE

Preliminary Report of Experimental and Clinical Study

CHRIST J. CHRISTY, M.D., BUFFALO, N. Y.

(From the State Institute for the Study of Malignant Diseases)

THE advent of modern endocrinology and biochemistry made possible a variety of estrogenic substances such as hormones or synthetic agents in the treatment of menopausal syndrome. The purpose of this paper is to report the writer's observation and clinical experience in the use of vitamin E as a therapeutic agent in a group of cases with severe symptoms of menopause. A large number of instances in the menopausal group of cases are seen at this clinic because of abnormal uterine bleeding induced by improper or prolonged dosages of estrogens. These patients are referred by their physicians with a suspicion of carcinoma of the uterus and of course are subjected to diagnostic curettage to rule out malignancy.

Consideration of uses and limitations of estrogenic therapy as outlined in a recent article by Novak¹ can be heartily endorsed, and such is the policy of the author in dealing with such cases. Estrogen is valuable at times in facilitating the hormonal adjustments of a large number of patients; however, like so many other valuable therapeutic agents, their prolonged and indiscriminate use is unnecessary and actually harmful. In regard to the so-called carcinogenic effect of estrogen, Novak¹ further states there has been considerable discussion as to whether or not excessive therapy can actually incite the development of cancer. Without reviewing this very broad problem, suffice it to say that the consensus is that no such hazard pertains to the clinical employment of estrogens in any customary therapeutic dosage. He further adds that since our knowledge of the possible carcinogenic role of the estrogens is still very incomplete, it is a wise policy to avoid unnecessarily large doses, and to eliminate such treatment altogether or hold it to a minimum for persons who harbor any so-called pre-cancerous lesions, or for those who have a clear-cut family history of cancer.

The question whether overstimulation of the aging endometrium by estrogens may enhance the evidence of carcinoma in human beings, as they have characterized the production of carcinoma in experimental animals, seems to be still unsettled, if one reads the vast amount of research on the subject.

The author's hope that vitamin E may be an effective remedy in treatment of the distressing symptoms of menopause was instigated by reading a report of a clinical and laboratory study on amenorrhea by Whitacre and Barrera.² This report deals with treatment of a large number of women internees in the Santo Tomas Internment Camp at Manila, Philippines, who were suffering from amenorrhea, probably due to severe psychic shock, worry, or fear. Due to a small supply of estrogenic substance available, ten patients of this group were given vitamin E in the form of wheat germ oil: a dose of 20 drops orally, three times daily, for a period of ten days preceding the expected menstrual flow. Eight of the ten patients had a menstrual period or a uterine bleeding. The exact role of vitamin E in the human organism is unknown, but Mattill,³ in reviewing the work on the subject, states that any definite connection of vitamin E with sex hormones and thyroid gland or any relationship to malignancy is not supported by the experimental evidence presented. He further states,

however, that the finding of hypoplastic thyroids in female E-deficient rats⁴ with return to normal appearance on administering vitamin E, suggests that thyrotropic as well as gonadotropic activity of the pituitary may be altered in the absence of vitamin E.

The author, impressed first with the favorable response obtained from vitamin E therapy in "War Amenorrhea," and second by our incomplete knowledge about the chemistry and physiology of this substance, began to investigate the effect or potentialities of vitamin E in the menopause, as therapy with estrogens in a large number of his cases, due to the cancerous nature of the lesion, was wholly contraindicated.

In this study of six months' time, vitamin E in 10 mg. tablet form as ephynal acetate (Roche), a synthetic preparation, was given by mouth to 25 patients ranging in age from 22 to 55 years. Of this group 12 had carcinoma of the cervix, one had adenocarcinoma of the fundus, one had malignant leiomyoma and sarcoma of the uterus, six had fibroids, one had carcinoma of the ovary, one had hemangio-endothelioma of the parametrium, one had post-menopausal bleeding after estrogenic therapy, one had dysfunctional uterine bleeding due to endocrine disorder, and one had endometriosis. No patient was treated who did not complain of severe symptoms of vasomotor instability.



Fig. 1.—Case No. 49898. Patient, aged 37 years. Artificial menopause, induced by x-ray and radium. Very marked relief of menopausal symptoms after a total dose of 550 mg. of ephynal acetate Roche). Vaginal smear (fuchsin stain), showing only a few degenerated epithelial cells; no vitamin E response.

The amount of the drug taken varied from 10 to 30 mg. a day, depending upon the degree of severity of symptoms, over periods of from one to six weeks. All patients in this study were handled in a uniform manner, and the clinical effectiveness of the drug was recorded by one observer. Of the 25 patients, one suffered from symptoms of natural menopause, five from surgical and irradiation menopause, eleven from x-ray and radium menopause, eight from radium menopause.

First reports of experimental use of this drug were astonishing. The entire group of cases responded to the treatment and showed either complete relief or very marked improvement with less frequency and less severity of the hot flashes and drenching perspiration, and a definite change for the better in their mood and outlook.

Of these 25 patients, seven reported complete relief of symptoms on dosages of 10 to 20 mg. daily over periods of from one to three weeks. Sixteen patients

reported very marked relief on 10 to 20 mg. daily over periods of from two to six weeks. A great reduction in the number of hot flashes per day was evident promptly upon taking the prescribed medication, and the patient's general condition greatly improved. These remarkable results obtained in these sixteen patients suffering with severe symptoms of menopause are sufficiently striking to justify calling attention to two of them. One patient (Case No. 46544) states: "I have noticed a diminishing of the hot flashes both in frequency and intensity." Another patient (Case No. 49671) writes: "Where six to eight flashes per day were very common before, I experience one per day after taking the medication."



Fig. 2.—Case No. 49987. Patient, aged 40 years. Artificial menopause, induced by x-ray and radium. Family physician gave patient several "shots" of estrogenic preparation twice a week. Vaginal smear (fuchsin stain) showing cornified epithelial cells, occasional leucocytes; full estius response. Suggested discontinuance of the "shots" and synthetic vitamin E prescribed instead. The replacement therapy with vitamin E was as effective as with the "shot" treatment.

It is the author's opinion that all of the latter group might have obtained complete relief on higher dosages, and subsequent indications point towards such a response, but at present they cannot, of course, be included with the complete relief group. In only two cases was treatment interrupted: Case No. 46661, with moderate relief, because of family and marital upset, and Case No. 43065, with slight or no relief, stopped treatment after a few days on 10 mg. daily. These patients were both advised to continue the treatment with comparatively higher dosage, 30 mg. per day. The author is of the opinion that both of these patients, with higher level dosage and under normal home life, will respond to treatment as did the rest of the group.

In discussing the results of therapy in menopause with synthetic vitamin E, it must be pointed out that the measure of clinical response was based largely on subjective findings. In a few instances, vaginal smears or endometrial biopsies, taken during the course of this study, revealed that vitamin E induced no change in the vaginal mucosa (Fig. 1) and endometrium. This was in contrast to the effect seen after estrogenic therapy on the vaginal epithelium (Fig. 2) and in the endometrium (Fig. 3).

Undesirable side reactions such as headache, nausea, vomiting, dizziness, soreness of the breasts, pelvic pain, and vaginal bleeding were not encountered in any of these patients.

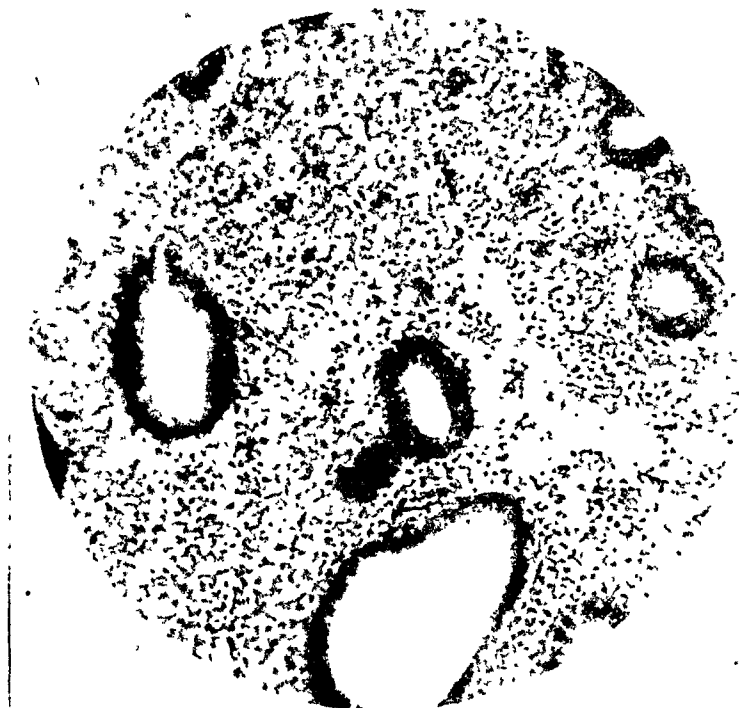


Fig. 3.—Case No. 51183. Patient, aged 50 years. Natural menopause three or four years previously. Five years ago, because of premenopausal symptoms, treatment by hypodermic injections of estrogenic preparation was begun by family physician at regular intervals and kept up because of skipping menstrual periods, menorrhagia, and metrorrhagia. Within the last few months this method of treatment was replaced by one tablet of estrogenic substance taken orally every morning. A few days before admission patient had a profuse vaginal hemorrhage. Endometrial biopsy showing endometrial glands are hyperplastic. The endometrial stroma shows intercellular hemorrhage; full estrus response.

Conclusion

This is a preliminary report of the clinical use of vitamin E in the treatment of menopausal syndrome. Vitamin E plays a physiologic role in women presenting symptoms of menopause. The nature of this action is not understood. The author believes that vitamin E has demonstrated its effectiveness in menopausal therapy by experimental and clinical application. The relief of symptoms in patients after administration of vitamin E could not be distinguished from that obtained with the natural or synthetic estrogens. In some cases vitamin E seems more effective in relieving the symptoms of vasomotor instability than estrogens. The chief advantage of the new drug over estrogen is in the fact that vitamin E is free of any stimulative effect or change on the genital system or in the parenchyma of the breast. It plays no possible carcinogenic role as the estrogens may do, and, due to the latter factor, vitamin E can be used freely in menopausal patients suffering from neoplastic disease. It produces no untoward aftereffects and is well tolerated.

Ephynal Acetate (Roche) used in this clinical investigation was supplied by Hoffman, LaRoche, Inc., through the courtesy of Dr. R. J. Floody.

References

1. Novak, E.: J. A. M. A. 125: 98, 1944.
2. Whitacre, F. E., and Barrera, B.: J. A. M. A. 124: 399, 1944.
3. Mattill, H. A.: J. A. M. A. 110: 1831, 1938.
4. Singer, Eleanor: J. Physiol. 87: 287, 1936.

SULFONAMIDE AND STILBESTROL THERAPY IN GONOCOCCAL VULVOVAGINITIS*

LUCILE R. HAC, PH.D., H. CLOSE HESSELTINE, M.D., FRED L. ADAIR,
M.D., AND MYRTLE B. CRUDIN, M.D., CHICAGO, ILL.

(From the Department of Obstetrics and Gynecology, the University of Chicago and the Chicago Lying-in Hospital, and the Chicago Municipal Social Hygiene Clinic)

FOR the past several years, we have been studying the problem of gonococcal infection in children.† Some of the preliminary results have been reported elsewhere.^{1, 2} This is the final report of our investigations of sulfonamide‡ therapy in this infection.

The use of cultural methods for the diagnosis of gonococcal vaginitis and proof of its cure have led to a truer concept of the incidence of the infection and is gradually eliminating the all too prevalent opinion that all or most vaginitis in children is gonorrheal in origin. Very frequently children recovering from respiratory infections show vaginal discharges. Smears of these discharges show many gram-negative cocci which are not gonococci, but which may be mistaken for them. On certain occasions, smears have been found to be particularly difficult to read when the predominating organism on culture was the streptococcus. Because of these difficulties, diagnosis should be based on culture as well as smear.

Older methods of local treatment of gonococcal vulvovaginitis have been notoriously inadequate. Either the infection persisted in spite of months of treatment, or, as has been reported frequently, many of the so-called cured cases relapsed a few weeks to several months after therapy had been discontinued. Since "cures" were usually based upon smear readings rather than cultures, it is very probable that the continuous presence of the gonococcus—though undetected in smears—accounted for the recurrence of the disease. We had the opportunity to observe the treatment and to study by culture 25 children who received six weeks of local therapy (mercurochrome). Only two (8 per cent) of the group had negative cultures which remained so for one year following therapy. Thirteen of the children had both positive smears and cultures throughout treatment. Ten had periods during and following therapy when the smears were negative although the cultures were persistently positive. This latter group according to older standards of "cure" might have been said to have had recurrences.

In order to evaluate accurately sulfonamide therapy, diagnosis was established by isolation and identification of the organisms before therapy was instituted. To be certain that there would be no recurrence,

*This work was done under a grant from the Albert B. Kuppenheimer Foundation, the Department of Obstetrics and Gynecology, the University of Chicago and the Chicago Lying-in Hospital.

†Most of the patients in this study were made available through Dr. Herman N. Bundesen, President of the Chicago Board of Health, and Dr. G. G. Taylor, Director of Syphilis and Gonorrhea Section of the Municipal Social Hygiene Clinic of Chicago.

‡The sulfonamides used in this study were furnished through the courtesy of the Medical Research Departments of (1) Winthrop Chemical Company, New York City, (sulfanilamide and sulfathiazole); (2) Merck and Company, Rahway, New Jersey, (sulfapyridine); and (3) Lederle Laboratories, Incorporated, Pearl River, New York, (sulfadiazine).

the determination of cure was based upon cultures and smears taken during treatment, and at regular intervals for one year following the termination of therapy. Such a long period of observation is almost impossible as a practical procedure, but in this study 125 children have fulfilled this strict criterion of cure.

Over 200 children were treated with the various sulfonamides: sulfanilamide, sulfapyridine, sulfathiazole and sulfadiazine. Forty-five had been deleted because they became delinquent and a full year of observation was impossible. At the time this study was necessarily discontinued, 30 children had been observed more than three months but less than six months. These cases, too, have been deleted. Ten children who had been observed for more than six months have been included; thus, in Table I, a total of 135 children who had 196 courses of treatment are considered in detail.

TABLE I. NUMBER OF PATIENTS AND COURSES OF THERAPY RECEIVED WHO WERE OBSERVED OVER ONE YEAR AFTER CESSATION OF THERAPY.

NUMBER OF PATIENTS		NUMBER OF COURSES	
99	One course of treatment	99	
36	More than one course of treatment	97	
	22 2 courses of treatment	44	
	9 3 courses of treatment	27	
	1 4 courses of treatment	4	
	2 5 courses of treatment	10	
	2 6 courses of treatment	12	
Total 135		196	

All of the children were ambulatory, and most of them were Negroes. They varied in ages from 11 months to 13 years; 20 were under 2 years of age, 54 under 5 years. Three of the girls had their first menstrual period during the year of observation. Eight patients had chronic infections, which had been treated previously by local therapy for varying lengths of time. All the other cases were in the acute stage.

Nine of the children became reinfected during observation and were retreated, and 20 children failed to respond to one or more of the drugs.

When this study was begun, only sulfanilamide and sulfapyridine were available. We expected to treat an equal number of children selected as impartially as possible with the two drugs. It soon became apparent, however, that sulfanilamide was not only not as efficacious in the treatment as sulfapyridine, but that it also produced "drug-fast" gonococcal strains which failed to respond to the other sulfonamides. For that reason, sulfanilamide was discontinued early. When sulfathiazole and sulfadiazine became available, these drugs were included in the study. As the use of sulfonamide therapy in gonococcal infections in both adults and children became more general, it was our observation that the number of new infections in children rapidly diminished. As a result, there were fewer cases for evaluation of sulfadiazine therapy. When the study was discontinued, 35 children had received sulfadiazine. Four of them had failed to respond to the drug or had recurrences after therapy had been discontinued, and only four had been observed over a year. Twenty-two had been observed three months, however, and were probably cured. They are included in the Tables IV and V, merely for comparison with the other drugs.

Table II lists each of the drugs in relation to the number of patients

TABLE II. NUMBER OF PATIENTS TREATED WITH EACH DRUG AND THE TOTAL NUMBER OF COURSES OF EACH DRUG GIVEN—ALL WERE OBSERVED FOR ONE YEAR AFTER THERAPY WAS STOPPED

DRUG	NUMBER OF PATIENTS			NUMBER OF COURSES	
	ONE DRUG	TWO OR MORE DRUGS	TOTAL	SAME DRUG REPEATED	TOTAL
Sulfanilamide	6	12	18	4	22
Sulfapyridine	42	19	61	9	70
Sulfathiazole	63	16	79	14	93
Sulfadiazine	2	2	4	0	4
Stilbestrol		6	6	1	7
Total	113	55	168	28	196
<div style="display: flex; justify-content: space-between; align-items: center;"> <div style="margin-left: 20px;"> 113 patients received 1 drug 22 { 15 patients received 2 drugs 3 patients received 3 drugs 4 patients received 4 drugs </div> <div style="margin-right: 20px;"> 113 30 9 16 </div> <div style="margin-right: 20px;"> } 55 </div> </div>					
Total	135		168		

who have been observed for one year. One hundred thirteen were cured by one or more courses of a single drug. Seven patients were reinfected twice. They were retreated with the same or a different drug and observed a full year after the time of reinfection before being discharged as cured. Ordinarily, if a child failed to respond to one drug, a different drug was used for the second course of treatment. Twenty-two patients received more than one drug, 15 received two drugs, three received 3 drugs and four received 4 drugs. When two or three sulfonamides failed to effect cure as was the case with a few children who received sulfanilamide, stilbestrol was tried finally. Since one child could receive one to five different drugs, the total of the numbers of patients on each of the drugs was 168. Occasionally, when a different drug was not available, a child received more than one course of the same drug. Thus, six children responded to a second course and two to a third course of the same drug. In all, the 135 children received 196 courses of the same or different drugs.

Methods

Diagnosis.—Diagnosis in every case was based on isolation and identification of the gonococcus by cultural methods.

Collection of Material for Bacteriologic Examination.—All the children were examined with a vaginoscope and materials for examination collected on two swabs. One swab was used for making the two smears. One smear was examined by the laboratory at the Municipal Social Hygiene Clinic, and the other at the laboratory at the Department of Obstetrics and Gynecology, University of Chicago, using Burke's modification of Gram's stain. The second swab was moistened with a few drops of nutrient broth and used immediately for inoculation of various special media. McLeod's chocolate agar gave the best results of the various media tried. Our procedure has been outlined in detail elsewhere.³ The inoculated plates were left at room temperature not longer than 5 hours, when they were transported to the laboratory where they were incubated at 35° C. in an atmosphere of 10 per cent carbon dioxide. Plates were examined at 24-hour intervals and discarded after 72 hours' incubation. Tetramethyl-p-phenylene diamine hydrochloride was preferred for the oxidase test. Oxidase positive or suspected colonies (very occasionally certain colonies did not give a definite positive oxidase test on primary isolation) were stained and examined microscopically. The organism was finally differentiated by carbohydrate fermentation.

Treatment and Criteria of Cure.—In Table III, the dosages of sulfonamides and stilbestrol are given. Treatment was withheld until the di-

TABLE III. SULFONAMIDE AND STILBESTROL DOSAGE IN GONOCOCCAL INFECTION IN AMBULATORY CHILDREN

AGE	WEIGHT	DAILY DOSE	NO. DOSES PER DAY	TOTAL DAYS	TOTAL DOSE
<i>Sulfanilamide</i>					
1 to 2 years	20 to 27 pounds	1.3 Gm. (20 gr.)	4	10	13.0 Gm.
2 to 5 years	27 to 42 pounds	2.0 Gm. (30 gr.)	4	10	20.0 Gm.
5 to 9 years	42 to 62 pounds	2.6 Gm. (40 gr.)	4	10	26.0 Gm.
9 to 11 years	62 to 100 pounds	3.0 Gm. (45 gr.)	4	10	30.0 Gm.
<i>Sulfapyridine, Sulfathiazole and Sulfadiazine</i>					
1 to 2 years	20 to 27 pounds	0.75 Gm. (11.3 gr.)	4	10	7.5 Gm.
2 to 5 years	27 to 42 pounds	1.5 Gm. (22.5 gr.)	4	10	15.0 Gm.
5 to 9 years	42 to 62 pounds	2.0 Gm. (30.0 gr.)	4	10	20.0 Gm.
9 to 11 years	62 to 100 pounds	2.5 Gm. (37.5 gr.)	4	10	25.0 Gm.
<i>Stilbestrol</i>					
All ages		0.3 mg. (0.45 gr.)	3	13 to 20	3.9 to 6.0 mg. (5.8 to 9.0 gr.)

agnosis was established by isolation of the gonococcus. Hemoglobin determinations (earlier the carbon monoxide method and later the Dare) were made before and during therapy. Smears and cultures, vaginal pH and blood for determination of drug concentrations were taken twice a week during treatment. Smears and cultures were continued twice a week for three months after therapy had been discontinued, and once a month thereafter, until the patient had negative cultures for one year. No provocative test was used. Marshall's method was used for determination of the concentration of sulfonamide in the blood.

Four doses of drug were given per day, and 10 days constituted a course of treatment. If a patient failed to respond to one course of therapy, a second course of the same drug was occasionally tried, but usually a different sulfonamide was used. Three days usually intervened between courses of treatment in order to allow time for reading the culture taken at the end of the first course of therapy. If a patient failed to respond after 2 or more courses of sulfonamides, stilbestrol was used. After sulfanilamide was discontinued, only one such case was encountered.

Results

Sulfonamide Therapy.—A comparison of the results obtained with the various sulfonamides is made in Table IV. Failures are considered from the standpoint of the particular drug or drugs that failed to effect cure. Although a patient may have required repeated courses of the same drug to bring about cure, the drug was considered to be successful and the previous course or courses of treatment were not listed as failures. Likewise, if a patient failed to respond to repeated courses of the same therapy, but was subsequently cured on another drug, the first treatment was considered to constitute one drug failure even though

TABLE IV. RESULTS OF SULFONAMIDE AND STILBESTROL THERAPY—THE NUMBER OF PATIENTS WHO RECEIVED ONE OR MORE DRUGS

DRUGS	NO. PATIENTS	NO. CURED	% CURED	NO. FAILURES	% FAILURES
Sulfanilamide	18	7†	39	11	61
Sulfapyridine	61	54‡	89	7	11
Sulfathiazole	79	70§	89	9	11
Stilbestrol	6	5	83	1	17
Sulfadiazine*	35	31	89	4	11

*Two observed one year, 33 observed for three months.

†Two patients required 2 courses.

‡One patient required 2 courses and 1 patient 3 courses.

§Three patients required 2 courses and 1 patient 3 courses.

repeated courses of the drug may have been used. Little emphasis should be placed on these cases, however, since it is impossible to be certain whether cure was due to the drug or to the self-limiting course of the infection.

If a patient became delinquent during or just following therapy while the cultures were still positive, the treatment was included as a failure even though the patient had not been observed long enough to effect a cure by other therapy.

Since some patients failed to respond to 2, 3 or 4 drugs, one patient could constitute a failure of 1, 2, 3 or 4 drugs. By this method of tabulation, the total numbers of failures resulting with any one drug could be determined. This might, however, lead to erroneous conclusions if the first drug selected for treatment caused the microorganism to become resistant to all subsequent sulfonamide therapy, as we believe was the case with sulfanilamide. In order to avoid such a fallacy, the first drug which failed to effect cure has been used as the basis for tabulation in Table V. Thus, each patient constituted one drug failure and that failure was credited to the initial therapy. The true figures lie probably some place between these two extremes.

In Table VI, the failures are considered individually. The complete treatment given in each case is listed and the time when cultures were

TABLE V. RESULTS OF SULFONAMIDE THERAPY WHEN ONLY INITIAL FAILURES ARE CONSIDERED

DRUGS	NO. PATIENTS	INITIAL FAILURES	% FAILURES
Sulfanilamide	18	11	61
Sulfapyridine	61	3	5
Sulfathiazole	79	5	6
Sulfadiazine*	35	2	6

*Two observed one year, 33 for three months.

TABLE VI. TREATMENT RECEIVED BY PATIENTS WHO WERE RESISTANT TO ONE OR MORE OF THE SULFONAMIDES

NO. PATIENTS	AGE YEARS	CULTURES +	THERAPY	RESULT
<i>Sulfanilamide Initial Therapy</i>				
520*	4	In 3 days		Delinquent +
356	6	Always	Sp.†	Discharged
385	5	In 3½ months	Sp.	Discharged
559*	1	Always	Sp.	Discharged
367	4	In 1 month	Sp., Sp.	Discharged
390	7	Always	Sp., Sp.	Delinquent +
547	7	Always	St.	Discharged
586	7	Always	S., Sp., St., Sb.	Discharged
589	8	Always	S., Sp., St., St., Sb.	Discharged
593	8	Always	S., Sp., Sp., St., Sb.	Discharged
650	6	Always	Sp., St., Sb., Sb., St.	Discharged
<i>Sulfapyridine Initial Therapy</i>				
498*	5	In 3 days		Delinquent +
550	2	Always	Sp., St.	Discharged
409*	2	Always	Sp., St., Sb.	Discharged
<i>Sulfathiazole Initial Therapy</i>				
716	8	In 2 months	Sp.	Discharged
741	8	In 2 weeks	Sp.	Discharged
760	3	In 2 weeks	Sp.	Discharged
685	2	Always	Sp., Sb.	Discharged
1,561	10	In 3 days	Sd., St.	Discharged
<i>Sulfadiazine Initial Therapy</i>				
1,564	4	In 3 days	St.	Discharged

*Previous local treatment.

†S. — Sulfanilamide, Sp. = Sulfapyridine, St. = Sulfathiazole, Sd. = Sulfadiazine, Sb. = Stilbestrol.

positive during or following treatment is stated. Those patients who failed to respond to therapy and whose cultures remained positive during the treatment period are designated in the column of "cultures +" as "always." This, of course, refers only to the drugs which did not effect cure and not to the final course of treatment. If a patient became negative during treatment, but later relapsed, the interval between positive cultures is given. The individual ages are indicated. The infection was ultimately eliminated in all patients who continued under treatment.

Discussion

In the treatment of gonococcal vulvovaginitis, there seems to be little choice between sulfapyridine, sulfathiazole or sulfadiazine either on the basis of initial or total failures. Response was almost identical: 89 per cent of cure in each series. Sulfanilamide is definitely contraindicated in the treatment of children, not only because it results in a greater percentage of failures (61 per cent), but also because it tends to produce strains of gonococci that are resistant to subsequent sulfonamide therapy. Both sulfanilamide and sulfapyridine produced more minor toxic symptoms than did sulfathiazole or sulfadiazine. Not once were severe toxic symptoms encountered in any of the series.

Stilbestrol was used with some measure of success in a few of the drug-resistant cases, but such cases should be rare when properly selected sulfonamide therapy is used. Five of the six children treated with stilbestrol did become negative during therapy and remained so. The sixth case responded to a combination of sulfathiazole and stilbestrol therapy. All the children that received stilbestrol showed some evidence of secondary sexual changes, but these regressed within a month after therapy had been discontinued. One such case has been described by us in detail elsewhere.²

There was considerable difficulty in determining whether some of the children had been reinfected or had a recurrence. If the child was known to have had contact with a member of the family or a playmate who had the infection, we were inclined to consider the possibility of reinfection, particularly if the cultures had become negative previously during treatment. Where no such contact was known, the treatment was considered a failure. We consider cultures taken during therapy to be most useful in evaluation of therapy. Ninety-five per cent of the patients that responded to one course of therapy had negative cultures three days after starting the therapy, whereas 65 per cent of the failures had positive cultures throughout treatment or did not become negative on culture until six to nine days after therapy was begun.

Of the 20 children considered failures on sulfonamide therapy, 11 had positive cultures throughout the courses of treatment. Of the nine who had negative cultures during treatment and later relapsed, six had positive cultures within two weeks after therapy was discontinued, one in a month, two within two months and one in three and one-half months. One child had a positive culture on the day she was to have been discharged after a year of observation. It was difficult to know whether this was a reinfection or a drug failure. No evidence of contact could be elicited. She was retreated with the same drug, and discharged cured a year later.

As a practical procedure, three months is probably long enough to observe children before they are discharged as cured, provided the diagnosis of cure is based on appropriate cultural studies. Patients under treatment and observation may be permitted to return to school as soon as cultures have become negative.

Although children require proportionately larger doses of drug and longer courses of therapy than do adults, young children responded to therapy as well as did the older ones. Of the 135 children studied, 54 were under 5, and 81 were over 5 years of age. Seventeen per cent of the children under 5, and 14 per cent of the children over 5 made up the group of "drug-failures."

Chronic infections did not respond to sulfonamide therapy as well as did acute cases. Eight children had chronic infections which had been treated previously with local therapy. Four of them (50 per cent) failed to respond to one or more courses of sulfonamides.

Hemoglobin determinations made before therapy was instituted showed variations from 56 to 98 per cent. Only 19 (14 per cent) of the children were below 70 per cent, and only one of the failures was in this group.

Determinations of concentrations of the drugs in the blood during therapy showed levels varying from a trace to 8.0 mg. per hundred cubic centimeters. The children that failed to respond to therapy did not have uniformly lower blood levels, than those that were cured by one course of treatment.

Conclusions

1. Diagnosis and criteria of cure of gonococcal vulvovaginitis should be based on cultures as well as smears.

2. Sulfathiazole and sulfadiazine are the drugs of choice in the treatment of this infection. Of 135 children treated with sulfanilamide, sulfapyridine or sulfathiazole and observed one year following therapy, equally good results were obtained with sulfapyridine and sulfathiazole whether response was based on cure (both 89 per cent), or upon initial failure (sulfapyridine 5 per cent, sulfathiazole 6 per cent). Sulfapyridine caused more minor toxic symptoms than did sulfathiazole. Sulfanilamide is definitely contraindicated because of the higher percentages of failures and because it tends to produce strains of gonococci which are resistant to sulfonamides. Of 35 children treated with sulfadiazine and observed three months following therapy, 89 per cent were cured and 6 per cent were initial failures.

3. Stilbestrol was useful in the treatment of sulfonamide-resistant cases.

4. Negative cultures for three months are probably sufficient criteria to establish a cure.

5. Patients under treatment and observation may be permitted to return to school as soon as cultures have become negative.

The authors take pleasure in acknowledging that this extensive study was accomplished by the willing and helpful cooperation by the following resident physicians of the Chicago Lying-in Hospital: Drs. Alice Campbell, Ruth Charles, Lester C. Crismon, Richard S. Donovan, David Feld, Eugene G. Free, A. F. Galloway, Robert G. Greene, Lewis L. Hall, G. Wardlow Hammond, Henrietta Herbolsheimer,

Jerome M. Hopper, S. Charles Kasdon, Franklin E. Kells, Jack Kight, David E. Kopans, Cecelia Kranaskas, George H. Lage, Robert C. Long, C. O. McCormick, Jr., Bernard Mortimer, Ruth O'Brien, Lester Odell, John M. Parrish, Leroy S. Pearce, Woodrow W. Pickardt, Morton W. Thompkins, Laura E. Weber, James D. Wharton, and others.

References

1. Adair, F. L., and Hac, L. R.: *New England J. Med.* 227: 465, 1942.
2. Adair, F. L., and Hac, L. R.: *M. Clin. North America*, Chicago Number 67: 67-81, 1943.
3. Hac, L. R., Hesseltine, H. C., Adair, F. L., and Hibbs, D. K.: *AM. J. OBST. & GYNEC.* 41: 98, 1941.

CRANIOTOMY*

With Review of Cases

J. IRVING KUSHNER, M.D., F.A.C.S., AND A. CHARLES POSNER, M.D.,
F.A.C.S., NEW YORK, N. Y.

(From the Obstetric Service of The Bronx Hospital, New York, N. Y.)

CRANIOTOMY is one of the most serious obstetric operations. Very little is written concerning its indications and technique. Frequently it is not used when it should be. Because it is gruesome and a mutilating procedure, few authors write in great detail on this important subject.

Too often have women, who give a history of premature rupture of the membranes, long hours of labor, and either repeated vaginal examinations or attempts at delivery, or both, been subjected to cesarean section with the delivery of a dead baby. Frequently, in order to save the lives of these women, a radical operation with removal of the uterus is done, thereby destroying the possibility of future childbearing. Many mothers have undergone the dangers of cesarean section to have presented to them a hydrocephalic child, or a child so damaged that it does not survive or, at best, is mentally deficient.

Craniotomy should be performed whenever the child is dead, unless it may easily be delivered by forceps. It should be done on hydrocephalic children where there is marked disproportion, or in other types of maldevelopment, provided the diagnosis is confirmed beyond a shadow of doubt and the mother cannot be delivered per vaginam. Craniotomy should not be done if the conjugata vera is below 6.5 cm., or where the pelvic canal is blocked by ovarian or uterine tumors, or when the cervix is fibrous or carcinomatous.

Incidence.—In this series of cases, from July, 1932, through June, 1943, at the Bronx Hospital, there were 22,705 deliveries. Of this number, 19 were delivered by craniotomy, a percentage of 0.084. (Table I.) Bailey and Williamson¹ reported 3 craniotomies out of 11,491 deliveries, a percentage of 0.026. Good² reported 8 craniotomies out of a total of 22,674 deliveries, a percentage of 0.36. Long and Stabnick³ report 29 craniotomies out of 12,292 deliveries, a percentage of 0.235.

*Read before The Bronx Gynecological and Obstetrical Society, Nov. 27, 1944.

Indications.—The indications for the craniotomies in this series are presented in Table II. It can be seen that cephalopelvic disproportion with a dead fetus was found in six cases. In one of these cases the disproportion was unrecognized and an attempt at forceps delivery having failed, a craniotomy was done. In two cases with a recognized flat pelvis, attempts at manual dilatation of the cervix resulted in a dead baby. One

TABLE I—SUMMARY OF THE CASES

CASE NO.	HOSP. NO.	AGE (YEARS)	GRAVIDA	PARA	PELVIC TYPE	HOURS OF LABOR			INDICATIONS FOR ORIGINAL OPERATION						INDICATIONS FOR CRANIOTOMY				
						1ST STAGE	2ND STAGE	RUPPT. MEMB.											
1	133474*	30	i	i	Normal	39	1½	39											
2	142531	24	i	0	Normal	31	3¼	26											
3	132538	37	iii	0	Normal	104	3¼	30											
4	92709	27	iii	i	Normal	60	¼	20											
5	65214	21	i	0	Normal	36		30											
6	63471*	22	i	0	Android	72	3	13											
7	63338	31	i	0	Android	10	5	40											
8	44945	30	ii	0	Flat	55	4	10											
9	39619	30	ii	0	Flat	12		22											
10	134316	28	i	0	Flat	30½	2¼	10											
11	120323	24	ii	0	Normal	23½	8	7											
12	128470	26	ii	i	Normal	6	3	4											
13	117471	26	i	0	Normal	10½	4½	4											
14	118007	40	v	ii	Normal	9½	1½	8											
15	98449	21	i	0	Normal	67	¼	67											
16	77717	21	i	0	Normal	98	1	40											
17	57931	24	i	0	Flat	42		39											
18	51804	35	i	0	Flat	40	¼	64											
19	41009	24	i	0	Normal	60													

*Maternal death.

†Unengaged vertex.

TABLE II—INDICATIONS FOR CRANIOTOMY

INDICATIONS	NO. OF CASES	MATERNAL RECOVERY	END RESULT DEATH
Unrecognized cephalopelvic disproportion; attempted forceps; dead fetus	1		1
Flat pelvis; cephalopelvic disproportion; attempted manual dilatation; dead fetus	2	2	
Flat pelvis; cephalopelvic disproportion; prolapsed cord; dead fetus	3	3	
Attempted forceps for occipitoposterior; Bandl's ring; dead fetus	4	3	1
Attempted forceps for occipitoposterior; dead fetus	3	3	
Hydrocephalus; disproportion	4	4	
Intrauterine death for 68 days; ineffectual labor pains; dead baby	1	1	
Bag induction for cervical dystocia; dead fetus	1	1	

*Version was also attempted in two cases, following failure of the forceps and before craniotomy was done.

of these was performed at home, and in the other, a craniotomy in the hospital gave rise to a rupture of the lower uterine segment. Prompt hysterectomy with the recovery of the mother occurred. In the other three cases, prolapse of the cord caused fetal death, and a craniotomy was the delivery of choice.

In seven cases forceps failed to deliver a baby which was in an occipitoposterior position, with a subsequent loss of the fetal heart. In four of these cases in the presence of a Bandl's ring the dead fetus was delivered by craniotomy under profound anesthesia. In the other three cases while there was no Bandl's ring, craniotomy was resorted to, version being contraindicated because of a tight uterus due to the length of time the membranes had been ruptured.

In our series, hydrocephalus occurred four times. In each case the diagnosis was confirmed by x-ray and a craniotomy was done because of the marked disproportion.

There was one case of fetal intrauterine death for 68 days with ineffectual labor pains, and one case of bag induction for cervical dystocia with the loss of the fetal heart at about five fingers' dilatation.

Length of Labor.—The length of labor of this group of patients varied between 107 and 9 hours. All of our cases had a history of early rupture of the membranes, the longest being 67 hours.

Maternal Mortality.—In this series of cases there were two maternal deaths, a percentage of 10.5. The details of these cases are shown in Table III.

TABLE III. MATERNAL MORTALITY

CASE NO.	INDICATIONS FOR CRANIOTOMY	CAUSE OF DEATH
143474	Failure of forceps for occipitoposterior; cephalopelvic disproportion; dead fetus	? Acute renal cortical necrosis
63471	Failure of forceps for occipitoposterior; Bandl's ring; dead fetus; intrapartum infection	Septic pelvic thrombophlebitis

Patient No. 143474, aged 33 years, gravida ii, para i. Membranes ruptured 39 hours, total labor 39½ hours, second stage 1½ hours. Intrapartum eclampsia. Craniotomy was done because of the failure of forceps to deliver an occipitoposterior with subsequent loss of the fetal heart. A congenital oxycephaly was delivered. The patient expired on the tenth postpartum day with signs which were interpreted by the medical consultant as being due to acute renal cortical necrosis.

Patient No. 63471, aged 22 years, primigravida. Total labor 72 hours, second stage, 3 hours, membranes ruptured 75 hours. Intrapartum infection. Failure of forceps for occipitoposterior. With the loss of

fetal heart, craniotomy was done. Patient ran a septic course due to a pelvic thrombophlebitis and expired on nineteenth postoperative day.

Technique.—A few words about the technique of craniotomy will not be amiss. In view of the shock, the patient should be typed and compatible blood should be ready for a possible transfusion. The procedure must be done under general anesthesia. Spinal anesthesia or caudal analgesia are definitely contraindicated. The patient should be re-draped and have a new vaginal preparation. Catheterization should be done before and after the operation to make sure that there has been no bladder injury. The procedure following the original description of Tarnier* should be strictly adhered to. After the delivery of the fetus, the placenta should be removed manually in order to save blood loss and to explore the uterus for possible rupture. This should be followed by a uterine packing. Chemotherapy should be started immediately.

Summary

Out of 22,705 deliveries at the Bronx Hospital, 19 were delivered by craniotomy, a percentage of 0.084. In these 19 cases there were two deaths, a percentage of 10.5.

Conclusion

1. Craniotomy is a necessary obstetric operation.
2. It is safer for the mother with a dead baby that cannot be delivered by forceps or version, or for the mother who is obviously infected.
3. It is the operation of choice for the delivery of malformations where vaginal delivery is difficult or impossible.

We are indebted to Meyer Rosensohn, M.D., F.A.C.S., Attending Obstetrician, The Bronx Hospital, for his helpful suggestions in the preparation of this report.

References

1. Cited by Long and Stabnick.
2. Ibid.
3. Long, J. P., Jr., and Stabnick, J. S.: South. M. J. 33: 1073, 1940.

1840 GRAND CONCOURSE
51 EAST 90TH STREET

*Bull. Acad. de med., Paris, 12: 1425, 1883.

ESSENTIAL DYSMENORRHEA—ITS TREATMENT WITH PAVATRINE*

A Preliminary Report

C. H. WEINBERG, M.D., NEW ORLEANS, LA.

AS NUMEROUS as are the theories of dysmenorrhea, the proposed medications are even more numerous.

It follows, of course, that since we are still ignorant as to the true cause of dysmenorrhea in the absence of pelvic pathology, and as dysmenorrhea is a symptom and not a disease, no one routine of treatment regularly gives any measure of success. For the most part, also, it is usually not possible to differentiate in any one individual the type

*B-diethylaminoethyl fluorine-9-carboxylate hydrochloride (Pavatrine). Supplied by G. D. Searle & Co.

of dysmenorrhea present, and there is always overlapping of the classified types: (a) the neurotic, (b) the obstructive, (c) the hypoplastic, and (d) the constitutional.

After many false starts, the author has had such improved results with the technique outlined below, that he feels that his findings are worthy of note.

It is freely admitted that pain is an individual concept; that the threshold of pain varies greatly, and that results are often untrustworthy when based on a history of symptomatic relief. In a later paper an attempt will be made to present scientific proof of the comparative value of antispasmodic drugs by means of a new type of apparatus now under construction. At present the findings are based upon symptomatic relief.

Method of Study

In the general series, patients were divided into two classes: (a) those whose chief complaint was menstrual cramps, and (b) those who, in the course of a routine gynecologic history, stated that menstrual pains were severe enough to cause them to alter their usual routine—either by remaining home from work and/or by making it necessary for them to remain in bed on the day or part of the day that their periods began.

In the present series, 141 cases have been reviewed. Of these, 41 could be explained on the basis of outstanding pathology that required operative correction or treatment, and are not included in the series.

Twenty cases complained primarily of painful menstruation, and these are divided into groups as shown in Table I.

Of those whose chief complaint was not painful periods, but who nevertheless suffered from severe enough pain to alter their usual activities, the division of cases is as shown in Table II.

TABLE I. CHIEF COMPLAINT—PAINFUL PERIODS

Single	8	Married	12
Average age	19	Average age	29
Disability:		Disability:	
Complete	3 (37%)	Complete	3 (25%)
Partial	5 (63%)	Partial	9 (75%)
Relief:		Relief:	
+++ to ++++	6 (75%)	+++ to ++++	8 (66+%)
+ to ++	2 (25%)	+ to ++	4 (33+%)

+++ and ++++ represent: no alteration in usual routine.

+ and ++ represent: relief, but some incapacity remained.

TABLE II. CHIEF COMPLAINT—OTHER GYNECOLOGIC SYMPTOMS

Single	0	Married	80
		Average age	33
		Disability:	
		Complete	16 (20%)
		Partial	64 (80%)
		Relief:	
		+++ to ++++	53 (66%)
		+ to ++	27 (34%)

For key to symbols, see Table I.

Method of Dosage and Control of Cases

Since dysmenorrhea cannot always be explained by organic pathology, and since the psychic effect of any "new medicine" is unquestionably great, it is necessary in any series to check each result carefully. Where a large group can be used at one time and placebos

substituted in a portion of the cases, control is easily enough established, but in private practice, where it is always necessary to furnish relief, this method is impractical. Therefore study was carried out in the following manner:

Each patient was given a prescription for pavatrine and instructed to take one tablet three times a day after meals, beginning three days before the onset of the expected period, and likewise on the first day of the period. If the period was delayed one or two days, the medication was to be continued in like manner, but no patient took pavatrine more than five days before the periods began.

Each patient was also given a second prescription for capsules, each containing phenobarbital $\frac{1}{2}$ grain, extract hyoseyamus $\frac{5}{6}$ grain, and amidopyrine 5 grains. She was told that this was an "emergency" drug and was instructed that she was not to use it unless her cramps were not relieved, but if her cramps were painful and she could not go about her usual activities, she was to take one capsule every four hours, as long as she remained uncomfortable. In this way an estimate of the amount of relief obtained by the pavatrine alone could be made, for if it was not necessary to take any of the capsules, then results were considered excellent. If, however, three or more capsules were necessary in any twenty-four hours, then obviously the pavatrine was of no measurable value.

No case is recorded in which this study does not cover a minimum of six menstrual periods, and as further check, one-half of the cases who responded well to pavatrine were asked to omit it for one month. In this latter group, there was return of their dysmenorrhea in every case.

In Table III the results in the series are demonstrated.

TABLE III. BREAKDOWN OF SERIES

Number of Cases:	100
1. Number with complete relief	48 (48%)
2. Number in which one capsule occasionally necessary	19 (19%)
3. Number in which two capsules necessary	23 (23%)
4. Number in which three+ capsules necessary (Failures)	10 (10%)
Therefore, relief (1 + 2)	67%

Rationale of Treatment

The etiology of dysmenorrhea is itself unknown. It is not the purpose of this paper to review the numerous theories as to the cause of dysmenorrhea. For our purposes, suffice it to say that the pain is certainly related to the uterine musculature or its innervation or both.

Pavatrine possesses both musculotropic and neurotropic action. Its action simulates that of morphine, but it has the marked advantage of being nonnarcotic.

Bickers¹ has demonstrated its antispasmodic effect and found it superior to other antispasmodic drugs. His method, however, employing the intrauterine balloon, involves the introduction of a foreign body into the uterus. In spite of the fact that a foreign body tends to increase the irritability of the uterus, unquestionably pavatrine, in this series, reduced the uterine contractions to a far greater extent than the other drugs investigated, with the exception of morphine.

Untoward Effects

Three of the cases were failures because of an apparent idiosyncrasy to the drug. This consisted of a severe trembling of the hands and a complete feeling of inability to control locomotion. As one patient expressed it, she felt as though she was "literally falling apart."

This sensation is unquestionably due to the marked relaxing effect of the drug. In such patients it should, of course, be discontinued.

Disadvantages

The drug should be begun a minimum of three days before the onset of the menstrual period. In irregular cycles the period will often present itself before any of the drug has been taken. In these cases the drug may be taken with the onset of the period, but it has been my experience that under these circumstances it loses much of its efficiency. On the other hand I have seen no harm in beginning medication too early. Patients may take pavatrine continuously for five days or more before the onset of the period without apparent side effects.

Selected Case Reports

Typical Successful Response.—Mrs. S. A., aged 23 years. Dysmenorrhea since menarche at 14 years of age. Periods regular. One child, aged 3 years. No relief from dysmenorrhea except during pregnancy and for first three months thereafter. With re-establishment of periods, menstrual “cramps” began.

Tried proprietary remedies and prescriptions by several doctors without relief.

No organic pathology present.

Placed on pavatrine, one tablet three times a day after meals, beginning three days before expected period. Complete relief for three months, then period began four days early. Took pavatrine on day of onset of period with partial relief only. Periods thereafter again regular. Pavatrine has relieved this patient with above exception for period of nine months.

Demonstrating Idiosyncrasy to Pavatrine.—Mrs. H. C., aged 26 years. Menarche at 13 years of age. Periods regular. Dysmenorrhea first day. Married three years, no children. No organic disease demonstrable.

Placed on pavatrine. After second dose became so dizzy that locomotion was impossible. Repeated attempts brought about the same symptom complex. Drug discontinued because of obvious idiosyncrasy.

Typical Failure of Response.—Mrs. C. L., aged 29 years. Two children. Periods regular. Dysmenorrhea since menarche.

Examination showed erosion of cervix, which responded to treatment.

Afterwards placed on pavatrine. First month necessary to take four capsules in twenty-four hours. Second month, slight relief, took two capsules. Third month, no apparent relief. Fourth month, no relief.

This case constitutes a complete failure.

Conclusions

A review of 100 cases of dysmenorrhea treated with pavatrine is presented.

The results seem to warrant that, with proper dosage, pavatrine is highly successful in relieving dysmenorrhea.

Reference

1. Bickers, W.: AM. J. OBST. & GYNEC. 42: 1023, 1941.
3439 PRYTANIA STREET

TEST CASE TO SHOW VALUE OF CERVICAL CYTOLOGY SMEAR IN UTERINE CANCER DIAGNOSIS*

J. ERNEST AYRE, M.D., W. A. G. BAULD, M.D., AND P. J. KEARNS, M.D.
MONTREAL, QUEBEC

*(From the Department of Obstetrics and Gynecology, Royal Victoria Hospital,
McGill University)*

CERVICAL cytology smears have been found to detect uterine cancer in lesions so minute as to be missed by the examining finger, the eye, or even the biopsy knife. Such a statement seems fantastic at first, and yet the illustrations accompanying this article prove it is not impossible. The explanation lies in the fact that any cancer lesion large enough to cause "spotting" desquamates specific cancer cells which appear in the blood and discharge, gathering at the external cervical os, to be spilled down into the vaginal secretions below.

Papanicolaou and Traut¹ were the first to describe specific cancer cells in the vaginal secretions of uterine malignancies. Meigs² corroborated their findings, confirming the high degree of accuracy described by the original investigators. Both groups admitted that the search for cancer cells was arduous and prolonged in some cases, at times requiring a study of three separate smears to arrive at the correct diagnosis. One of us (J. E. A.)³ has recently described a modification of the technique whereby smears taken routinely from the external cervical os showed larger concentrations of cancer cells. The search for the diagnostic cancer cells was, therefore, facilitated and accelerated, rendering the test more efficient.

The cytology of smears prepared from the cervical os is different from that found in the vaginal smear. This is true of normal cases as well as in cancer. In the normal cases, larger numbers of cervical cells, squamous and glandular, and of the endometrial cells from above are found in the secretions at the cervical portal. Most cancer of the genital tract arises from either the cervix or the fundus uteri. Therefore, it seems only natural that larger concentrations of the telltale malignant cells may be found at the external os, the source of the spill. Therefore, small early growths manifesting only occasional desquamation and spotting, which may require prolonged study for diagnosis by the vaginal smear, yield a more speedy decision in the rapid detection of cancer cells in the cervical cytology smear. While three slides may be required to diagnose some cases by the vaginal smear one is usually sufficient in the cervical cytology smear.

Case Report

The patient, a 42-year-old American woman, was admitted to the Women's Pavilion of the Royal Victoria Hospital on April 9, 1944. She gave a history of having been delivered of a child by instruments eighteen months previously. A year later a checkup revealed a small erosion from which a biopsy was taken by her physician in New York

*Aided by a grant from the Banting Research Foundation.

State. The biopsy was reported as showing a cervical malignancy, and the patient was referred to Dr. W. A. G. Bauld, head of the Cancer Clinic of the Women's Pavilion. Pelvic examination, on admission, revealed a moderately enlarged mobile uterus attached to a hypertrophic, freely movable cervix. Dr. Bauld stated at this time that he could find no cervical lesion demonstrable clinically, other than the usual small circular erosion about the external os. Cervical cytology smears were taken and studied. The first smear was reported positive for cancer. On the basis of the smear findings, coupled with the history of the cervical biopsy, a panhysterectomy was performed.*



Fig. 1.—Showing cells found in cervical os smear. Note variable size and conformation of nuclei, also some vacuolation in cancer cells.

Pathologic Report.—Grossly the specimen consisted of a generally enlarged uterus with cervix attached, measuring 18 by 13 by 8 cm. The cervix appeared hypertrophic with a small circular eroded area surrounding the external os. Repeated sections of the cervix showed no ulcerated or indurated portion. In view of the suspicion of cancer aroused by the history and the vaginal smear findings, four separate cervical biopsies were taken at 12, 3, 6, and 9 o'clock, respectively. None of these exhibited any gross evidence of cancer. The other organs showed no relevant disease.

The microscopic findings were of interest. The first segment of cervix examined showed evidence of cystic cervicitis with a normal appearing squamocolumnar junction (Fig. 2). The second segment examined, however, showed a different picture. The squamous epithelium appeared normal up to a point approaching the squamocolumnar area. Here the character of the squamous epithelium exhibited a distinct and abrupt change, the epithelium becoming thicker and the cells showing an hyperplastic appearance. The cytology of this area exhibited a tendency to immaturity, the cells presenting many large and numerous small pyknotic nuclei. Some of these showed evidence of mitosis. There was no marked invasion of the cervical stoma, but the subepithelial tissues in the hyperplastic zone showed a definite round-cell infiltration (Fig. 3).

The other pelvic tissues showed no evidence of involvement, although the myometrium showed an independent lesion in the nature of a deeply spreading adenomyosis.

Dr. Bauld, in replying to the physician who had referred the patient to him, summarized the case as follows: "Mrs. L. referred by you has been treated by hysterectomy. I confirmed your diagnosis prior to operation by vaginal (cervical) smears which showed definite cancer cells. I could not localize the site of the lesion as the cervix was perfectly healthy in appearance. On this reasoning, I felt that operation would complete the treatment more effectively than radiation. I did a total hysterectomy and bilateral salpingo-oophorectomy. Test of the cervical tissue postoperatively showed a very minute superficial cancerous lesion of the cervix, one of the earliest in our records. I think we can look forward to an almost certain cure."

*We usually make it a practice to confirm smear findings by the biopsy before resorting to operation or radiotherapy.



Fig. 2.—First cervical biopsy showing cystic cervicitis with normal appearing squamocolumnar junction.



Fig. 3.—Second cervical biopsy showing change in character of squamous epithelium approaching squamocolumnar junction. Note superficial noninvasive cancer (Bowen's disease).

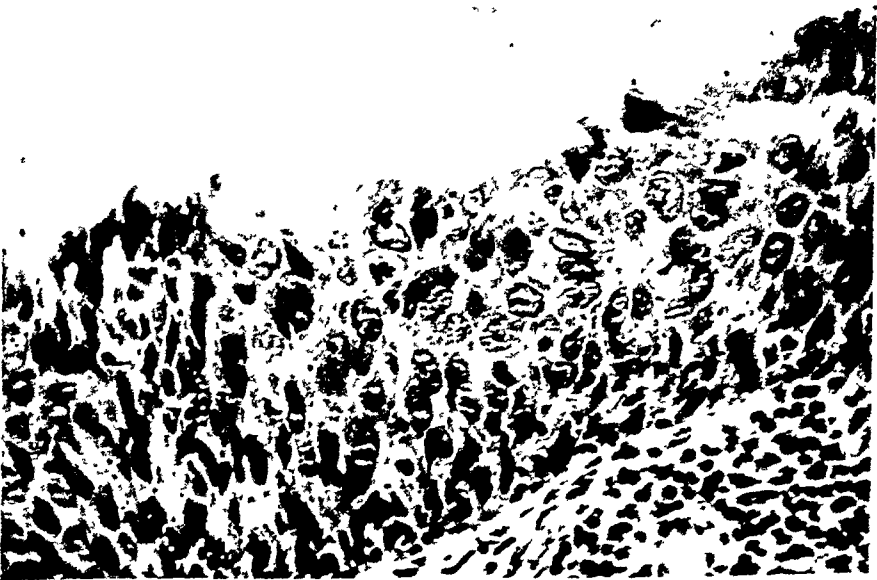


Fig. 4.—High-power photomicrograph of cancerous area. Note resemblance of cells in smear to those along the surface.

Criteria of Diagnosis

Considerable study of normal and abnormal vaginal and cervical cytology is necessary to enable one to accurately differentiate the cancer cell from the benign cell. In general, the criteria as outlined so beautifully by Papanicolaou and Traut in their monograph⁴ have been followed. In brief, the finding of blood and pus cells scattered among normal squamous cells with more or less numerous atypical cancer cells showing specific nuclear changes (multilobulation, multinucleation, anisocytosis, pyknosis, and multiple chromatin granulations) is significant.

The morphology of the cancer cells found in different cases is extremely variable. But the cells from any one case are usually found to be similar to the cells found in the actual tissue biopsy in that case (Figs. 1 and 4).

Technique

The technique is that described in "A Simple Office Test for Uterine Cancer Diagnosis."³ The cervical cytology smear is taken, using a curved glass pipette following exposure with a bivalve speculum. The mucous and blood present at the external os of the cervix or from the surface of the lesion is drawn up into the pipette by suction. This is transferred to a glass slide suitably labeled. The mucus is spread over the slide to prevent the smear being too thick. The slide is then immediately immersed in a solution of ether and alcohol 95 per cent (equal parts). Up to this stage, the test may be taken in the office or clinic, wherever the patient is first seen. The bottle containing the smears is then sent to the cytology laboratory for the more complicated process of staining and expert interpretation.

The simplicity of the test is important, as the inevitable delay associated with an advisement of hospitalization for biopsy is eliminated. Therefore, the case arousing only suspicion of malignant possibilities in the physician's mind is given the benefit of a "surface biopsy" without waiting until signs of more advanced growth indicate that hospitalization and biopsy have become an obvious and imperative conclusion.

Observation

The opinion of the chief gynecologic pathologist (P. J. K.) is that the lesion is an early superficial squamous-cell carcinoma, which at this early stage is still noninvasive. This would appear to fall into the group of early cancer lesions described as "Bowen's disease." Some pathologists have argued that the lesion is not cancer until there is invasion. It is our conception, however, that lesions so early and so minute as this one appears to be should be considered as cancer in a preinvasive form. No doubt if the disease were diagnosed very early more often, it would be found to be in this relatively benign preinvasive stage.

Summary

A case has been presented in which an early cervical cancer was detected by the cervical cytology smears while the lesion was so localized as not to be detectable by the trained eye or the finger, and 50 per cent of the surgical biopsies failed to show it.

It would appear that the vaginal and cervical cytology smears are of definite value in the diagnosis of very early as well as advanced cases of uterine malignancies.

References

1. Papanicolaou, G. N., and Traut, H. F.: *AM. J. OBST. & GYNEC.* 42: 193, 1941.
2. Meigs, J. V., et al.: *Surg., Gynec. & Obst.* 77: 449, 1943.
3. Ayre, J. E.: *Canad. M. A. J.* 51: July, 1944.
4. Papanicolaou, G. N., and Traut, H. F.: *Diagnosis of Cancer by Vaginal Smears*, New York, 1943, Commonwealth Fund.

PAROVARIAN CYST CAUSING DYSTOCIA

WENDELL DOWNING, M.D., AND LAWRENCE O'TOOLE, M.D., LE MARS, IOWA
(From the Le Mars Clinic)

IN 1939 the authors,¹ in a review of the literature since 1873, reported 62 cases of parovarian cysts complicating pregnancy, seven of which produced dystocia. A personal case was reported in which an intraligamentary cyst resulting in dystocia was treated by aspiration through the vaginal wall, permitting a spontaneous delivery to occur. In 1940 the following almost identical case was encountered.

Case Report

Mrs. A. S., aged 37 years, para vii, admitted to the hospital May 20, 1941, gave the following history: In October, 1939, the patient had had a spontaneous abortion at three months followed by a third-degree retroversion which was corrected by a pessary. After the sixth month of her present pregnancy she had four prenatal examinations. No unusual symptoms or signs were elicited, and a vaginal examination was not made. On Nov. 20, 1940, she was seen at her home in the country by one of us. Labor had been in progress for nine hours. Vaginal examination revealed complete effacement and dilatation but the fetal head did not advance with her pains. A soft fluctuant mass the size of a baseball was palpable in the cul-de-sac on vaginal and rectal examinations. With a syringe and large needle inserted through the posterior vaginal wall in the midline, 150 c.c. of clear fluid was aspirated from the cyst. The head then promptly descended and the patient was delivered of a 10-pound infant. Her puerperium was normal and at eight weeks post partum no pelvic mass was palpable. Surgical removal of the cyst was advised but not agreed to. On May 18, 1941, the patient was again seen in the office with a complaint of pain and left lower quadrant soreness of several days' duration. She also complained of rectal and bladder pressure. Abdominal examination revealed tenderness deep in the left lower quadrant. On vaginal examination a soft tender mass was just palpable to the left and posterior to the uterus. The leucocyte count was 16,000. A diagnosis of a cyst with a twisted pedicle was made and immediate surgery advised. For two days the patient was more comfortable, then the pain again became severe. On admission to the hospital her leucocyte count was 6,000 and her general condition was good.

An exploration through a left paramedian incision showed the uterus to be normal in size and position. A mass, 12 cm. in diameter, was present in the cul-de-sac, being adherent to the peritoneum by fibrinous exudate. The mass was a left parovarian cyst with a narrow pedicle 7 cm. long, twisted two complete turns counterclockwise, the pedicle arising from the left broad ligament just beneath the fimbriated end of the left tube. The thick-walled cyst and pedicle showed hemorrhagic changes; the cyst contained 150 c.c. of serosanguinous fluid. The fimbriated end of the tube was obliterated by fibrous adhesions. The ovaries and right tube were normal. The cyst and left tube were removed and all raw surfaces peritonealized. An appendectomy was also done. The patient made an uneventful recovery and was dismissed from the hospital on the eleventh postoperative day.

Aspiration of a cyst impacted in the pelvis during labor is a safe and simple procedure. Removal of the cyst at an early date is always advisable.

Reference

1. Downing, Wendell, and O'Toole, Lawrence: J. A. M. A. 112: 1798, 1939.

INTRAPERITONEAL NABOTHIAN CYST

ROBERT T. FRANK, A.M., M.D., NEW YORK, N. Y.

MRS. N. C., aged 22 years, was referred to me because of attacks of right lower abdominal pain, correctly ascribed to slight torsion of the pedicle of a right ovarian cyst.

Examination showed a healthy young woman. The genital tract was nulliparous, uninfected; the uterus anteverted, of normal size; the right ovary enlarged to orange size, tender; the left adnexa normal. The cervix was normal.

In November, 1943, through a paramedian suprapubic incision an orange-sized bluish thin-walled cyst of the right side was excised and a prophylactic appendectomy performed.

Examination of the field preceding closure revealed a thin-walled colorless cyst projecting above the contour of the uterus on its posterior surface (Fig. 1). The cyst was 3 by 2 by 1 cm. The origin of this cyst puzzled me. At this level, Gartner's cysts are found not in uterine tissue but in the broad ligament. Cysts due to adenomyosis would contain chocolate fluid. Without further speculation, however, the cyst was removed by excising it together with a thin layer of uterine muscle, and the resulting defect was closed by suture. Convalescence was uneventful.

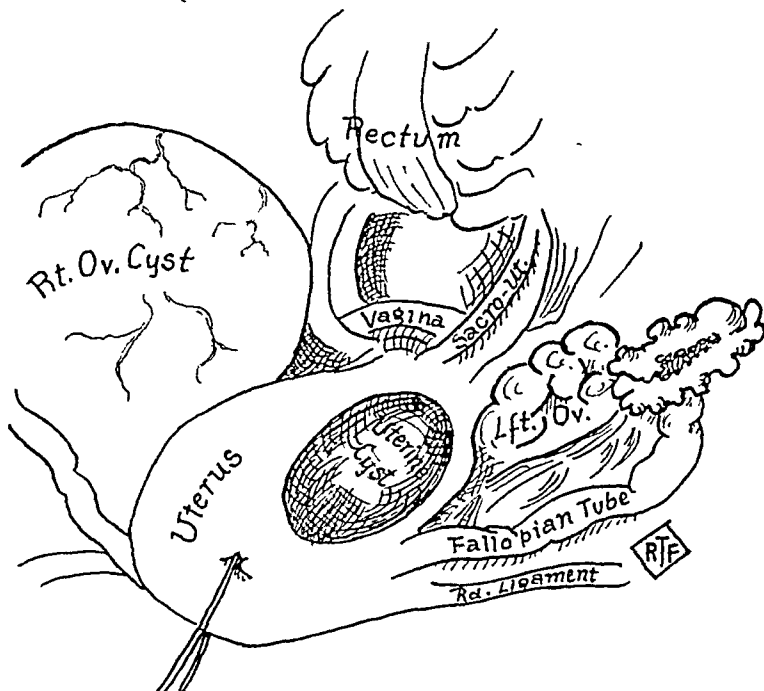


Fig. 1.—Uterus pulled to right exposing nabothian cyst on posterior surface of uterus above sacro-uterine ligaments.

To my surprise the uterine cyst was reported as “cervical tissue with nabothian follicles and chronic inflammation.” When I informed Dr. S. Otani, the Associate Pathologist of Mount Sinai Hospital, from what location I had removed the specimen, he too was astounded, but when we reviewed the specimen together, no other interpretation was possible (Fig. 2).

Comment.—The intraperitoneally presenting cyst in the lower posterior uterine wall was due to dilatation of cervical glands which grew and developed outward and upward instead of downward toward the



Fig. 2.—Photomicrograph of lining of uterine cyst. Typical cylindrical cervical epithelium.

portio as is usual. The possibility that these glands originally were abnormally located seems likely because I have never previously encountered, nor have I seen any mention in the literature, of a similar localization, in sharp contrast to the great frequency of nabothian cysts of the portio.

AVULSION DEFECTS OF THE SCALP OF THE NEWBORN INFANT

Medicolegal Implications

WILFRED J. FINEGOLD, M.D., AND EUGENE B. SCHUSTER, M.D., PITTSBURGH, PA.

(From the Departments of Obstetrics and Pediatrics, Montefiore Hospital)

THE importance of the recognition of congenital defects of the scalp lies in the fact that they may be mistaken for a result of obstetric trauma. Finkelstein¹ refers to the necessity of a clear differentiation of these congenital defects from traumatic lesions for medicolegal reasons. He cites several lawsuits instituted against obstetricians. Some of the early reports suggest that prenatal trauma is the cause of these scalp defects. Abele² considered his case due to an injury sustained by the mother ten weeks before birth, and Schatz³ attributed his case to an exostosis of the maternal pelvis.

Although these defects can be found on any part of the newborn infant, they are most commonly found on the scalp. The lesions are of comparatively rare occurrence. Rogatz and Davidson,⁴ in 1942, found that not more than 125 cases had been reported. In 1930, Terruhn⁵ reviewed 76 cases, in which the head was involved in almost half. Abt⁶ reported 37 cases up to 1917.

The common type consists of single or multiple pinhead to coin-sized defects of the scalp over one of the parietal bones. They are irregularly oval in shape and have punched-out margins which may present more or less evidence of healing.

Most writers, including Abt,⁶ attribute the lesions to inflammatory adhesions between the external layers of the skin and the amnion. As the amniotic

fluid accumulates, the adhesions are put under tension and stretch into the so-called Simonart's bands. When these bands are torn loose from the fetal integument, a defect remains. Because these lesions are consistent with this probable etiology, we choose the term "avulsion defects" to differentiate them from the congenital dysplasias and aplasias of the skin of the newborn infant also commonly referred to as "skin defects."

Abt⁶ concluded from microscopic examination that growth of squamous epithelium, smooth muscle, and fat are retarded in the fetal areas involved. The presence of well-developed connective tissue (possible beginning healing?) led him to believe that the defects were caused during early embryonal life.



Fig. 1.—Appearance of "congenital" skin defect, two days after delivery.

Case Report

Mrs. E. G., a white private patient, primigravida, aged 25 years, was seen at the twelfth week of pregnancy. The expected date of confinement was Aug. 15, 1944. The past history, family and general history were all negative. The prenatal course was uneventful. On August 17, after a twelve-hour labor, she was delivered of a living, 8-pound male baby. Delivery was facilitated by a left mediolateral episiotomy and outlet forceps. The infant was normal except for the following defect:

At the vertex of the scalp two ulcerated areas were seen, one on each side of the midline. That on the left was 1 cm. by 1 cm. in diameter and that on the right 1.3 cm. by 2 cm. The edges were puckered by beginning cicatrization and the floor appeared raw and irregular with what seemed to be hair follicles situated in the purple-red tissue. No evidence of inflammation was present. Healing progressed rapidly and epithelization was complete on the tenth day post partum. At this time a few fine hairs were seen in the otherwise unbroken layer of glabrous skin.

Treatment consisted of applications of 2½ per cent sulfathiazole ointment for two days; then cod-liver oil ointment until epithelization was complete. No dressings were applied.

The mother immediately accepted the explanation of the defect. The father was suspicious and inferred that the lesion was caused by some negligence on the part of the nursing staff or by an "instrument injury" produced by the obstetrician. Only when the scalp healed was the father at last placated. There was no litigation.

Summary

A case of "congenital" skin defect of the scalp of a newborn infant is reported. A brief résumé of the literature is presented, the accepted explanation of the lesion is discussed and a more specific nomenclature suggested. The importance of these lesions lies in the fact that, through being mistaken for traumatic obstetric injuries, they may be the grounds for litigation.

References

- Finkelstein, E.: Berl. Klinik. No. 168, 1902.
Abele: Med. Cor.-Bl. d. württemb., ärztl. Vereins 5: 1, 1835.
Schatz, M.: Monatschr. f. Geburtsh. 34: 110, 1869.
Rogatz, J., and Davidson, H. B.: Am. J. Dis. Child. 65: 916, 1943.
Terruhn, E.: Arch. f. Gynäk. 140: 341, 1930.
Abt, I.: Am. J. Dis. Child. 14: 113, 1917.

MEDICAL BUILDING.

Necrology

HIRAM NAHUM VINEBERG, M.D., a pioneer gynecologist of New York City, died at his home there, May 4, 1945, at the age of 88 years. Born in Russia, Dec. 20, 1857, he came to Cornwall, Ontario, Canada, at the age of five. At 18 he entered McGill Medical School and graduated in 1878 with its highest honor, the Holmes Gold Medal. After a sojourn in London, he went as ship's surgeon to New Zealand, practiced his profession there and then in Hawaii, returning to Canada for a period when he became interested in gynecology and subsequently studied in Berlin, Prague, and Vienna before he settled in New York in 1886.

Dr. Vineberg was attending gynecologist at the Mt. Sinai Hospital in New York and served there from 1893 until his retirement in 1921, after which he was made a consultant. He was also connected in this capacity with Beth Moses and Montefiore Hospitals. A member of many specialist and other medical societies and a Fellow of the American College of Surgeons, he had been a Vice-President of the American Gynecological Society and President of the New York Obstetrical Society. Dr. Vineberg was the author of many contributions to this JOURNAL and its predecessor, as well as to other medical publications. In 1943 a memorial volume was published in his honor by the Mt. Sinai Hospital.

Department of Reviews and Abstracts

Selected Abstracts

Anatomy, Anomalies, Etc.

Power, R. M. H.: The Exact Anatomy and Development of the Ligaments Attached to the Cervix Uteri, Surg., Gynec. and Obst. 79: 390, 1944.

This article is the first of a series of three dealing with the ligaments and fascia attached to the cervix, and concerns itself with the anatomy of Mackenrodt's ligament. The other two articles, to appear at some future date, relate to the embryology and development of the pelvic fascia and to its clinical significance. A brief review of Mackenrodt's life and his original description of the cardinal ligaments is given.

The author derived his material from four cadavers, two in old age, and two in their sexual prime. In addition, numerous fetuses in various stages of development were examined. In summary the cardinal ligament is described as a connective tissue capsule having an inverted U shape. It is attached medially to the anterior and posterior marginal walls of the cervix and laterally to the white line and fascia of the levator ani. On its posterior superior surface lies the uterine vein, while the artery is anterior. Laterally, an obliquely extending fascial reef is present which deflects the uterine artery anteriorly and the ureter laterally. At the extreme lateral aspect of the ligament the artery crosses the ureter at right angles. The anterior and posterior surfaces are described. Of interest is a foramen or gap between the ligament and the fibers from the levator ani. The triangular space between the three surfaces of the ligament is filled with areolar tissue and smooth muscle.

L. M. HELLMAN.

Olds, J. M., Swanker, W. A., and Josephson, J. E.: Uterine Malformation, South. M. J. 37: 436, 1944.

Failure of union in the Müllerian ducts leads to various degrees of uterine deformity. A double uterus is very rare, bicornuate and septate uteri relatively common. The case reported is one of complete double uterus. At operation the left uterus was small but connected to the cervix, and from its upper left cornua emerged a relatively normal-looking tube, and near the fimbriated end was an ovary with multiple follicle cysts. On the right a small uterus was seen densely adherent to the posterior peritoneum and connected with a greatly dilated tube filled with old blood. There was no connection between this uterus and the cervix. Pathologically the right uterus and tube showed a small atrophic uterus lined with secretory endometrium, the tube being the site of a hematosalpinx.

WILLIAM BICKERS.

Abortion

Croisier, M.: The Preventive Use of the Sulfonamides in the Treatment of Abortion, Schweiz. med. Wchnschr. 73: 1465-1470, 1943.

The author firmly believes that there should be no intervention in cases of abortion when fever is present or in cases of induced abortion even if they are not septic. The favorable outcome in the large majority of cases of uncomplicated abortion is

an argument against the use of large doses of the sulfonamides for prophylactic purposes. At the Lausanne Maternity the author has used "sulfa" therapy prophylactically and therapeutically in cases of abortion. In the febrile cases there was a diminution in the number of days of fever as compared with patients who did not receive sulfa drugs. However, no difference was observed in the control and sulfa group who had no complications. The prophylactic use of sulfa drugs not only did not prevent a fatality but in some cases tended to produce a persistence of mild fever for a long time. Therefore the author says that the preventive use of sulfa drugs in cases of abortion is at present without any value.

J. P. GREENHILL.

Weilerstein, Ralph W.: *Intrauterine Pastes*, J. A. M. A. 125: 205, 1944.

The author reports his findings reviewing some abortion fatalities and inquiries in connection with the use of soap pastes. The toxic effects are listed in two groups, systemic and local. The systemic effects, such as hemolysis, jaundice, pulmonary embolism, and septicemia, are the most marked. Sterility (tubal occlusion) and hemorrhage are the two most common local reactions. Peritonitis is not an uncommon finding. The author states that he has been informed by physicians who have used this paste that it is ineffective in 50 per cent of the cases. Appropriate steps have been taken to control the use of soap pastes by the institution and successful completion of legal actions directed at the manufacturers of these products under the Federal Food, Drug, and Cosmetic Act.

WILLIAM BERMAN.

Teare, Donald: *Air Embolism in Criminal Abortion*, Lancet 247: 242, 1944.

Teare reports a fatality induced by air embolism following an attempt to induce an abortion of a purported three months' pregnancy. A soap and water mixture were introduced into the vagina by means of the enema syringe. The 18-year-old unmarried girl became immediately cyanotic and collapsed. When the police arrived fifteen minutes later, the patient had expired.

Autopsy revealed a uterus enlarged to the size of a five to six months' pregnancy and contained a male fetus weighing 17.5 ounces. The membranes had been stripped off up to an inch above the lower attachment of the placenta. The placental site contained vessels 0.5 cm. in diameter. The upper part of the inferior vena cava, the right side of the heart and pulmonary artery were found to be pink and filled with bubbles. No bubbles were detected on the systemic side of the circulation. The bubbles were iridescent. The author states that the volume of liquid expelled at one squeeze of an ordinary enema syringe is approximately 43 c.c. and into an enclosed space it is delivered at a pressure which easily reaches 28 cm. of mercury or 380 cm. of water. When the ball-valve end of a syringe was dipped into the frothy soapy water, it was found that about 25 c.c. of air passed through the syringe for every squeeze of the bulb.

C. E. FOLSOME.

Gynecologic Operations

Flax, H. J.: *The Use of Cotton Sutures in Lower Abdominal Surgery*, Bol. Asoc. méd. de Puerto Rico 36: 170, 1944.

Continuous cotton thread sutures were used successfully by H. J. Flax in the peritoneal and fascial closure of lower abdominal wounds, thus speeding up the time of operative technique to equal that of catgut. Single unit, number 50, cotton thread is recommended; where stronger suture is needed, this thread is doubled or tripled. One case of incisional hernia in a right rectus incision is reported. This was due to faulty technique with poor approximation of the lower end of the anterior rectus layer, rather than to the use of a continuous cotton suture.

The advantages of cotton thread are: low cost, easy availability; remains stable on exposure to heat and moisture and is easily sterilized; a high coefficient of friction allowing the tying of secure knots; and, that it does not irritate the wound,

since it produces no tissue reaction, thus affording greater comfort to the patient. The only disadvantage to the use of cotton is its lower initial tensile strength as compared with catgut, silk or linen; but this is offset by greater retention of tensile strength in the tissues.

J. P. GREENHILL.

Phelan, G. W.: The Use of Carbolic Acid (Phenol) in the Treatment of Bartholinian Abscess, *Am. J. Surg.* 64: 28, 1944.

After incising the Bartholinian abscess and evacuating the pus, the author advocates packing the cavity with pure phenol for one and one-half minutes. It is then swabbed with alcohol and packed with iodoform gauze. The method has been employed for ten years with gratifying results.

FRANK SPIELMAN.

Decker, A., and Cherry, T. A.: Culdoscopy, *Am. J. Surg.* 64: 40, 1944.

"Culdoscopy" is the term applied by the authors to the direct inspection of the intra-abdominal pelvic organs through the cul-de-sac, using a cytoscope-like instrument called the "culdoscope." With the patient in the knee-chest position, the cul-de-sac is punctured by means of a trochar and cannula, the trochar removed and the instrument introduced. To facilitate inspection of the pelvis a cannula attached to a self-retaining screw tip is applied to the cervix so that the uterus may be manipulated when desirable. Indications for the procedure are sterility, "small ovarian disease," unruptured ectopic, endometriosis, etc. Caudal and local anesthesia are recommended to prevent pain.

FRANK SPIELMAN.

Labor, Management, Complications

Valenzuela, Raul Garcia: Induction of Labor, *Bol. Soc. chilena de obst. y ginec.* 8: 226, 1943.

The author has used the following method: at 6 A.M., castor oil, 45 Gm., quinine sulfate, 0.6 Gm.; at 8 A.M., soapsuds enema, quinine, 0.3 Gm.; then every half hour, alternately thymophysin 5 units (0.5 c.c.) and quinine 0.3 Gm. until 20 units of thymophysin and 1.20 Gm. of quinine have been taken.

In most cases the indication was prolongation of pregnancy beyond normal limits: in 33 of the 56 cases the prolongation varied from 4 to 14 days, seventeen having a pregnancy of 290 days or more. Five patients who were admitted with weak pains or premature rupture of membranes requested acceleration of labor to shorten their hospitalization. Exceptional indications were two cases of eclampsism (one with prolonged pregnancy), two of ovular infection, one of uterine fibroma, and one with contracted pelvis (both with prolonged pregnancy).

The series included 25 primiparas and 31 multiparas, and the presentation was vertex 54, breech 2. The entire treatment was given in 37 cases, while only the first doses were needed in some. In five it was impossible to produce efficient contractions, and labor occurred in from 7 to 35 days. In six an obstetric intervention was necessary for delivery and a second induction was needed in four. Spontaneous labor as immediate result of the method occurred in 44 cases (78.57 per cent).

J. P. GREENHILL.

Cabrera, H.: Induction of Labor by Watson's Method, *Bol. Soc. chilena de obst. y ginec.* 8: 212, 1943.

The author uses the following method which resembles that of Watson.

(1) Castor oil, 30-60 Gm. (2) Quinine, 0.3 or 0.6 Gm. (3) Soapsuds enema. (4) Pituitary extract, 2.5 to 5 units. (5) Quinine, 0.3 Gm. (6) Pituitary extract, same dose as previously. (7) Continuation of quinine and pituitary until four doses of each are given. The interval between the drugs in this schedule varies from half an hour to one hour. If labor starts, treatment is stopped.

The indications of the method are prolonged pregnancy, infection, membranes ruptured some days previously in which infection is feared, missed labor, habitual death of fetus, and fetal gigantism.

The method was used in 64 patients: 19 primiparas and 45 multiparas. Absolute success was obtained in 4 primiparas and 27 multiparas, or 48.5 per cent. Relative success and relative failure occurred in 11 per cent each, and absolute failure in 28.5 per cent.

There were three fetal deaths, 4.6 per cent, not including a fetus of 1,400 Gm. which died subsequently from prematurity. Three women had simple purulent endometritis and one puerperal pyemia; all recovered. One woman died, 1.5 per cent.

J. P. GREENHILL.

Muñoz, Luis: *Aburel's Method. Its Value for Induction of Labor*, Bol. Soc. chilena de obst. y ginec. 8: 87, 1943.

The author reports the results obtained in 28 cases: 15 personal, and the others from various hospitals in the city.

The method consists of injection of a saturated solution of sodium chloride (35 per cent) into the ovular cavity by the transabdominal route, the puncture being made in the midline halfway between the umbilicus and the pubis, after preliminary emptying of the bladder. Local anesthesia is unnecessary. Tincture of iodine is applied to the skin and a lumbar puncture trocar, or a large needle for intramuscular injections may be used. To make sure of being in the ovular cavity, a few cubic centimeters of amniotic fluid are aspirated; usually the fluid flows spontaneously from the needle.

The effect of the injection is not immediate, the time needed varying from forty-five minutes to twenty-four hours. Labor is of normal duration. The mechanism of action of the method is unknown. It might be similar to that of the sodium ion on the intestine, which according to Ringer's experiments stimulates the smooth muscle fibers. The method offers no danger to mother or fetus and causes no complications. However, the heart beats of the fetus must be watched.

The method has been used in cases of chronic nephropathy aggravated by pregnancy, of pre-eclampsia and eclampsia, and of prolonged pregnancy. In 12 cases the induction method of Watson had failed even when repeated three times.

The fetuses were alive in 16 of the 28 cases when the method was applied, and 3 died, but the deaths could not be attributed to the method. One patient was operated upon, and four had a labor of over twenty hours. Five had retention of the placenta; one had hemorrhage and manual extraction. Twenty-two had a normal puerperium, five a complication of simple endometritis, and one died of scarlet fever.

J. P. GREENHILL.

Costa, Nicanor Palacios: *Partial Symphysiotomy*, Bol. Soc. chilena de obst. y ginec. 8: 94, 1943.

The author states that the method is based on total section of the symphysis fibrocartilage and partial section of the arcuate ligament, the remainder of the latter being separated by forced abduction of the thighs which are maintained in that position. One of the major advantages of this technique is limitation of the use of the knife, thus avoiding possible injury to the urethra, bladder, and cavernous bodies. When the pubic extremities open, the sacroiliac joints act as hinges, their bony surfaces separating, thanks to the softening of the anterior sacroiliac ligaments which are distended. It has been experimentally proved that the separation of the pubic ends after section of the symphysis is 3 to 4 cm., but it may be increased to 5 cm. without rupture of the sacroiliac ligaments. Clinically, the separation needed does not exceed 4 cm.

The correct indication for symphysiotomy implies spontaneous birth. Zarate has given as absolute indication for his operation relative bony dystocia with a conjugate above 7.5 cm. in flat pelvis and of 8 cm. in the generally contracted pelvis in multiparas with cephalic presentation, ruptured membranes, and complete dilatation or dilatable cervix. He has given as relative indications primiparity, anom-

alies of uterine contraction, incomplete dilatation of the cervix, dystocia of the soft parts, fetal suffering, and slight amniotic infection. He has given as contraindications any bony dystocia with a conjugate of less than 7.5 cm. in flat pelves and 8 cm. in generally contracted pelves, infected primiparas, or those with grave fetal suffering, and dystocia of contraction or of the soft parts.

The statistics of Hospital Rawson show that dystocia was treated with symphysiotomy in 115 cases with two deaths, or 1.73 per cent, and with cesarean section in 93 cases with 15 deaths, or 16.12 per cent.

J. P. GREENHILL.

O'Connell, John E. A.: *Maternal Obstetrical Paralysis*, Surg., Gynec. and Obst. 79: 374, 1944.

Five interesting cases of protrusion of the lumbosacral disk associated with pregnancy and labor are described. In each instance paralysis or weakness of the lower extremity was present and all were markedly improved by operation. The author feels that this syndrome with resultant sciatic or femoral pain and/or paresis is a more common complication of pregnancy than generally suspected. It is suggested that hormonal relaxation of the lumbosacral joint may be responsible for the liability of the disk to rupture.

L. M. HELLMAN.

Ealing, Mildred I.: *Amyoplasia Congenita Causing Malpresentation of the Fetus*, J. Obst. & Gynaec. Brit. Emp. 51: 144, 1944.

The author reports a case of amyoplasia congenita in a multipara in which resulted a persistent transverse position of the fetus which was finally rotated to a breech and delivered as such. Amyoplasia congenita is a condition of unknown etiology, characterized by congenital symmetrical joint rigidities of varying degree unassociated with inflammatory change. The condition was associated with hydramnios which is a common concomitant of this fetal abnormality.

WILLIAM BERMAN.

Items

Society of Obstetricians and Gynecologists of Canada

The first annual meeting of this Dominion-wide organization, the Society of Obstetricians and Gynecologists of Canada (La Société des Obstétriciens et Gynécologues du Canada) was held at Montreal, June 15 and 16, 1945, under the chairmanship of Dr. Léon Gérin-Lajoie, its first president. It has a membership of about ninety Fellows representing all parts of the Dominion and has designated the JOURNAL as its official organ of publication. The complete proceedings of its initial meeting will appear in a subsequent issue.

The officers for the current year are Dr. William A. Scott of Toronto, President, Dr. James Goodwin of Toronto, Secretary.

Correspondence

Complicated Knot of the Cord

To the Editor:

Recently a woman was delivered in this hospital of a 7-pound $3\frac{1}{2}$ -ounce male infant with an unusual knot in the umbilical cord. The knot was caught over the posterior shoulder, and difficulty was encountered in delivering the shoulders. The prenatal and postpartum courses were uneventful for both mother and child.

The following pathologic report was given:

Gross Description.—Specimen consists of a placenta which is round and measures $17\frac{1}{2} \times 16 \times 2$ cm. The cotyledons are intact. There appears to be a firm band of connective tissue around the periphery of the placenta. The membranes are intact; the cord is slightly eccentric in its attachment being 5 cm. from the nearest edge. The cord appears normal in diameter. However, about 36 cm. from the placenta, a complicated knot is formed in which the cord passes through three loops upon itself. This knot is approximately 8 cm. from the infantile attachment.

Microscopic Examination.—Section through the placenta shows some small foci of early calcification and the usual obliterating vascular changes. No abnormal histologic findings were encountered.

Diagnosis.—Placenta showing an unusual true knot in the umbilical cord."

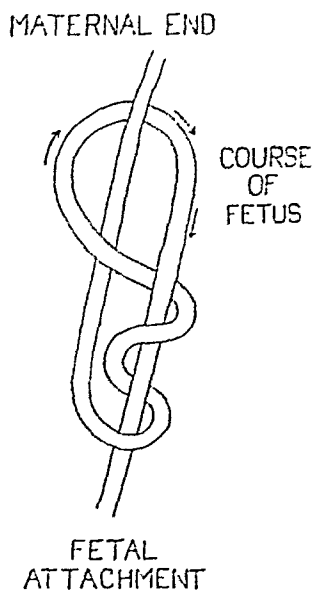


Fig. 1.

According to Ashley¹ the structure was identified as the "Stevedore Knot" (No. 522). However, it is evident from the identification of the fetal (free) and placental (standing) attachments that the knot was formed by the fetus passing through two loops of cord, Fig. 1, instead of merely wrapping the free (fetal) end around the standing (placental) end and passing the free end through the loops as would ordinarily be done.

This case seems to be more complicated than any of the umbilical knots recently described by Hennessy.² Moreover, when we trace the course of the fetus in producing this anomaly, it is almost impossible to imagine just how the knot was formed; whereas, if the course had been reversed, the explanation would be relatively simple.

References

1. Ashley, C. W.: The Ashley Book of Knots, Garden City, N. Y., 1944, The Country Life Press, p. 85.
2. Hennessy, J. P.: AM. J. OBST. & GYNEC. 48: 528, 1944.

CAPTAIN E. C. H. SCHMIDT, M.C.

CORAL GABLES, FLA.
DEC. 30, 1944

ROSTER OF AMERICAN OBSTETRICAL AND GYNECOLOGICAL SOCIETIES*

(Appears in January, April, July, October)

- American Gynecological Society.** (1876) *President*, Edward A. Schumann, Philadelphia, Pa. *Secretary*, Howard C. Taylor, Jr. 842 Park Ave., New York, N. Y. Annual meeting cancelled.
- American Association of Obstetricians, Gynecologists and Abdominal Surgeons.** (1888) *President*, Lewis F. Smead, Toledo, Ohio. *Secretary*, James R. Bloss, 418-11th Street, Huntington, W. Va. Annual meeting Hot Springs, Va., Sept. 1944.
- Central Association of Obstetricians and Gynecologists.** (1929) *President*, John H. Moore, Grand Forks, N. D. *Secretary-Treasurer*, W. F. Mengert, Dallas, Tex. Annual meeting not announced.
- South Atlantic Association of Obstetricians and Gynecologists.** (1938) *President* Oren Moore, Charlotte, N. C. *Secretary*, T. J. Williams, University, Va. Annual meeting cancelled.
- A. M. A. Section on Obstetrics and Gynecology.** *Chairman*, Philip F. Williams, Philadelphia, Pa. *Secretary*, William Mengert, 2211 Oak Lawn Ave., Dallas Tex. Meeting cancelled.
- New York Obstetrical Society.** (1863) *President*, R. A. Hurd. *Secretary*, R. G. Douglas, 530 East 70th St., New York City. Second Tuesday, from October to May, Yale Club.
- Obstetrical Society of Philadelphia.** (1868) *President*, Charles A. Behney. *Secretary*, John B. Montgomery, Pro tem, 1930 Chestnut St., Philadelphia, Pa. First Thursday, from October to May.
- Chicago Gynecological Society.** (1878) *President*, James E. Fitzgerald. *Secretary*, Herbert E. Schmitz, 25 East Washington Ave., Chicago, Ill. Third Friday, from October to June, Hotel Knickerbocker.
- Brooklyn Gynecological Society.** (1890) *President* Chas W. Mueller. *Secretary*, William T. Daily, 142 Joralemon St., Brooklyn, N. Y. First Friday, from October to May, Kings County Medical Society, 1313 Bedford Ave., Brooklyn, N. Y.
- Baltimore Obstetrical and Gynecological Society.** (1929) *President*, Lawrence Wharton. *Secretary-Treasurer*, John W. Haws, 9 E. Chase St., Baltimore, Md. Meets quarterly at Maryland Chirurgical Faculty Bldg.
- Cincinnati Obstetrical Society.** *President*, Edward Friedman. *Secretary*, Carroll J. Fair, Cincinnati, Ohio. Third Thursday of each month.
- Louisville Obstetrical and Gynecological Society.** *President*, Layman A. Gray. *Secretary*, E. P. Solomon, Hegburn Bldg., Louisville, Ky. Fourth Monday, from September to May, Brown Hotel.
- Portland Society of Obstetrics and Gynecology.** *President*, Charles Hunt. *Secretary-Treasurer*, Karl H. Martzloff, 808 Medical Dental Bldg., Portland, Ore. Last Wednesday of each month.
- Pittsburgh Obstetrical and Gynecological Society.** (1934) *President*, James S. Taylor. *Secretary*, Joseph A. Hepp, 121 University Place, Pittsburgh, Pa. First Monday of October, December, February, April, and June.
- Obstetrical Society of Boston.** (1861) *President*, George Van S. Smith. *Secretary*, Paul A. Younge, 101 Bay State Road, Boston, Mass. Third Tuesday, October to April, Harvard Club.
- New England Obstetrical and Gynecological Society.** (1929) *President*, Roy J. Hefferman, Brookline, Mass. *Secretary*, Fred J. Lynch, 475 Commonwealth Ave., Boston, Mass. Meetings held in May and December.
- Pacific Coast Obstetrical and Gynecological Society.** (1931) *President*, Goodrich C. Schauffer. *Secretary-Treasurer*, William Benbow Thompson, 6253 Hollywood Blvd., Los Angeles, Calif.
- Washington Gynecological Society.** (1933) *President*, James R. Costello. *Secretary*, Geo. J. Ellis, 1150 Connecticut Ave., N.W., Washington, D. C., Fourth Saturday, October to May.

*Changes, omissions, and corrections should be addressed to the Editor of the JOURNAL. The number after the name is the year of founding.

- New Orleans Obstetrical and Gynecological Society.** (1924) *President*, E. L. Zander. *Secretary*, R. A. Grasser, 2700 Napoleon Ave., New Orleans, La. Meetings held every other month.
- St. Louis Gynecological Society.** (1924) *President*, S. A. Weintraub. *Secretary*, Joseph A. Hardy, Jr., 4952 Maryland Ave., St. Louis, Mo. Meetings second Thursday, October, December, February, and April.
- San Francisco Gynecological Society.** (1929) *President*, R. Glenn Craig. *Secretary*, D. G. Morton, California University Hospital, San Francisco, Calif. Regular meetings held second Friday in month from October to April, University Club, San Francisco, or Claremont Country Club, Oakland, Calif.
- Texas Association of Obstetricians and Gynecologists.** (1930) *President*, T. F. Bunkley. *Secretary*, J. McIver, 714 Medical Arts Bldg., Dallas, Tex.
- Michigan Society of Obstetricians and Gynecologists.** (1924) (Formerly the Detroit Obstetrical and Gynecological Society.) *President*, Owen C. Foster. *Secretary*, Milo R. White, 2799 W. Grand Blvd., Detroit, Mich. Meetings first Tuesday of each month from October to May (inclusive).
- Obstetric Society of Syracuse Hospitals.** (1938) *President*, Edward C. Hughes. *Secretary*, Nathan N. Cohen, 713 E. Genesee St., Syracuse, N. Y. Meets second Tuesday of September, November, January, March, and May. Suspended for the duration.
- Alabama Association of Obstetricians and Gynecologists.** *President*, J. M. Weldon, Mobile, Ala. *Secretary*, Eva F. Dodge, Montgomery, Ala.
- San Antonio Obstetric Society.** *President*, I. T. Cutter. *Secretary*, S. Foster Moore, Jr., San Antonio, Tex. Meetings held first Tuesday of each month at Gunter Hotel.
- Seattle Gynecological Society.** (1941) *President*, Gerhard Ahnquist. *Secretary*, Roger E. Stewart, Stimson Bldg., Seattle, Wash. Meetings held on third Wednesday of each month.
- Denver Obstetrical and Gynecological Society.** (1942) *Secretary*, Emmett A. Mechler, 1612 Tremont St., Denver, Colo. Suspended during war.
- Wisconsin Society of Obstetrics and Gynecology.** (1940) *President*, Roland S. Cron. *Secretary*, Robert E. McDonald, 425 E. Wisconsin Ave., Milwaukee, Wis. Meetings held in May and October.
- San Diego Gynecological Society.** (1937) *President*, Geo. D. Huff. *Secretary*, D. Dalton Deeds, 2001 Fourth Ave., San Diego, Calif. Meetings held on the last Wednesday of each month.
- North Dakota Society of Obstetrics and Gynecology.** (1938) *President*, Ralph E. Leigh, Grand Forks. *Secretary*, G. Wilson Hunter, 807 Broadway, Fargo, N. D.
- Virginia Obstetrical and Gynecological Society.** (1936) *President*, A. L. Carson, Jr. *Secretary*, L. L. Schamburger, 628 State Office Bldg., Richmond, Va. Next meeting not announced.
- Columbus Obstetrical and Gynecological Society.** (1944) *President*, Zeph J. R. Hollenbeck. *Secretary*, Wynne M. Silbernagel, 9 Buttles Ave., Columbus Ohio. Meetings held last Wednesday of each month.
- Nassau Obstetrical Society.** (1944) *President*, Arthur C. Martin. *Secretary*, William S. C. Dolan, 2870 Northern Blvd., Manhasset, N. Y. Meetings, bi-monthly from October to May.
- Bronx Gynecological and Obstetrical Society.** (1924) *President*, Jacob Clahr. *Secretary-Treasurer*, J. Irving Kushner, 1840 Grand Concourse, New York, N. Y. Meetings, fourth Monday monthly from October to May.
- Washington State Obstetrical Society.** (1936) *President*, John H. Fiorino Everett. *Secretary*, H. H. Skinner, Yakima. Meetings, first Saturday of April and October.
- Kansas City Obstetrical and Gynecological Society.** (1922) *President*, J. Milton Singleton. *Secretary*, Richard C. Helman. Meetings, third Thursdays, September, November, January, March, and May, University Club.
- Los Angeles Obstetrical and Gynecological Society.** (1914) *President*, George E. Judd. *Secretary*, Carl E. Krugmeier, 2200 West Third Street, Los Angeles, Calif.
- North Carolina Obstetrical and Gynecological Society.** (1932) *President*, Frank Locke, Winston-Salem. *Secretary*, Wallace B. Bradford, Charlotte, N. C. Meetings semiannually.

American Journal of Obstetrics and Gynecology

VOL. 50

AUGUST, 1945

No. 2

Original Communications

FURTHER EXPERIENCES IN THE USE OF TRANSPLANTED ABDOMINAL FASCIA IN THE RELIEF OF STRESS INCONTINENCE

W. E. STUDDIFORD, M.D., F.A.C.S., NEW YORK, N. Y.

(From the Sloane Hospital for Women)

INCONTINENCE of urine occurring under circumstances which raise intra-abdominal pressure, such as sneezing, coughing, etc., is a fairly common complaint among gynecologic patients. In many of them this symptom is of minor consequence and often is not admitted unless the patient is directly questioned in regard to her urinary control.¹ The term generally accepted for this condition is that of stress incontinence, said to have been coined by Eardley Holland.² It has also been called diurnal incontinence,³ but less aptly since, while it occurs most commonly during the daylight hours, it is related directly to effort on the part of the patient.

While in the majority of instances this symptom is so slight that it constitutes only a minor annoyance, it sometimes develops to such a degree that the patient, on the slightest muscular effort, discharges large quantities of urine. Such individuals are only continent when lying down or sitting quietly and, even under these circumstances, as can be readily demonstrated on the examining table, there is lack of urinary control if the intra-abdominal pressure is raised. It is with this extreme degree of stress incontinence, particularly if previous surgical efforts at relief have failed, that this report is chiefly concerned.

The etiological factors in the background of this condition are well known, consisting most commonly of the injuries which occur to the supporting structures of the pelvic organs during the process of parturition. If such injury is concentrated on the supporting tissues of the bladder neck and upper urethra, stress incontinence will appear immediately (Refer to Case 2, Group II). On the other hand, if the injury is mostly to the supporting structures of the posterior part of the bladder trigone the symptom may not appear until many years later, usually at about the time of the menopause. This is the most common sequence of events.

NOTE: The Editors accept no responsibility for the views and statements of authors as published in their "Original Communications."

The involutionary changes at the menopause have a marked influence on the development of this symptom, and sometimes, in nulliparous women, appear to be solely responsible for its appearance. It has long been known that spayed female dogs exhibit urinary incontinence, and veterinary surgeons were the first to point out that this disorder could be controlled by the administration of stilbestrol. Geist and his co-workers⁴ have reported on the beneficial effects of estrogen therapy in human subjects exhibiting urinary symptoms during the menopause. Case 4, Group I, illustrates the advantages as well as the disadvantages of this form of treatment for stress incontinence. Finally, in rather rare instances, individuals are encountered who give a history of stress incontinence since early childhood. Their disability usually is increased to a marked degree by parturition. Case 1, Group II, illustrates this rather uncommon background. A congenital weakness in the supporting structures must be assumed in these patients. The etiological factors therefore may be traumatic, involutional or hormonal, congenital, or a combination of two or more of these factors.

The physical characteristics of women suffering from severe stress incontinence are surprisingly similar. In order to prevent urinary leakage, they avoid physical activity as much as possible, and, therefore, tend to become adipose and flabby. This tendency does not improve their risks as surgical patients. As a rule it cannot be improved before operation. Only by relieving the patient of her disability can she be made more active, with a resultant improvement in her general condition.

Pelvic examination may reveal a variety of lesions due to injury or relaxation of the pelvic supporting structures. In addition, other gynecologic conditions, such as uterine fibroids, may be present. However, the lesion which is essentially associated with the symptom is the urethrocele. This is exemplified by the patients in whom previous surgery has given excellent results as far as the general pelvic supporting structures are concerned, but in whom the urethrocele alone recurs, associated with a continued lack of urinary control. This is illustrated by six of the seven cases to be presented in Table I. An uncomplicated urethrocele often escapes casual examination, the bladder and urethra appearing to be well supported. On requesting the patient to cough or strain, a typical displacement takes place; the bladder neck and upper urethra bulge downward with the lower vaginal wall, which rotates through an arc whose center is at the lower border of the symphysis, so that the urethral orifice points upwards and forwards. At the height of this movement a thick stream of urine is ejected with considerable force, sometimes for several feet. Bonney² has pointed out that the escape of urine can be prevented by placing a finger on each side of the bladder neck and holding it behind the symphysis. He offers this as a test to determine whether a successful result can be attained by surgery. A sound placed in the urethra further aids in demonstrating the degree to which the upper urethra and bladder neck can be displaced backward and downward from behind the symphysis. Cystoscopic examination yields little information. With the patient reclining and at rest, no abnormalities of bladder capacity can be found. The usual "waterfall effect" at the internal urethral orifice is absent, indicating a loss of tone in the sphincter. On straining, the anterior part of the trigone will be seen to fall backward and downward, producing a cone-shaped urethral orifice. The significance of this finding will be discussed later.

To understand the lesion which constantly accompanies stress incontinence, a brief review of the supporting mechanism of the female urethra and bladder is necessary. The trigone of the bladder rests upon a sheet of tissue which separates it from the anterior vaginal wall. This sheet is composed of areolar tissue, in which are embedded nonstriated muscle fibers running in an antero-posterior direction. Because of its gross characteristics it is called the pubocervical fascia, although it differs microscopically from the structure of true fascia. It is attached, in front, to the back of the symphysis and behind, in the midline, to the cervix at its junction with the vagina, while on each side it blends with the corresponding transverse cervical ligament. Laterally, it can be traced upward to the pelvic side wall where it is attached along the white line, which is the line of fusion of the visceral and parietal layers of the endopelvic fascia.

The pubocervical fascia is separated from the base of the bladder by a plane of cleavage, which is utilized in separating the vagina from the bladder in complete hysterectomy. Any weakness in the posterior part of this sheet can be demonstrated and repaired during this operation. The inferior aspect of this sheet lies against the anterior vaginal wall, a plane of cleavage intervening which is made use of in the repair of systocele. It is perforated at its anterior extremity by the urethra to which it contributes a sheath of tissue which surrounds this structure in its downward course, and which, when traced laterally, attaches itself to the back of the lower pubic body. The bladder itself receives an investing layer of fascia derived from the superior aspect of the pubocervical layer. It is along the line of cleavage between this investing layer of fascia and the bladder muscularis that the peritoneum is freed from the vesicle fundus in the Waters extraperitoneal cesarean section. The anterior aspect of the bladder with its covering of fascia is attached to the back of the pubic bone only by thin fibers. It can be separated from the bone with great ease down to the attachment of the pubocervical sheet, where immediate resistance is met because of the firm attachment of the latter to the bone.

It seems evident that the lesion permitting the development of urethrocele must consist in the sudden tearing or gradual attenuation of the most anterior part of the pubocervical fascia, together with its descending investment on the urethra, thus allowing the bladder neck and urethra to herniate downward and backward through the defect. Cystoscopic observation suggests that the posterior segment of these structures is mainly involved. Whether there is associated injury to the inner and outer longitudinal and middle circular muscle layers of the urethra and to the internal sphincter is a matter of controversy. Some students of this condition, notably Kelly,¹² maintain that the incontinence is due to injury of the intrinsic muscles of the upper urethra and bladder neck, while others, notably Watson¹ and Bonney,³ maintain that the intrinsic muscles in these regions, having lost their fibromuscular support, tend to lose tone and to become ineffective. Kennedy⁵⁻⁷ has recently conducted an extensive investigation of the intrinsic musculature of the urethra and bladder neck by an ingenious contrivance, and finds extensive alterations in the contour of the urethra and the bladder neck, when stress incontinence is present; he assumes that this must be due to changes in the intrinsic muscles. He concludes, however, that the most important factor in the defect is the injury to the supporting mechanism which allows the musculature to become ineffective. The bulk of evidence points to the fact that the intrinsic musculature of the urethra and the bladder neck

play only a secondary part in the production of stress incontinence. The primary factor is injury or attenuation of the supporting fascia.

In order to understand the relationship of urethrocele to the symptom of stress incontinence, it is necessary to review the modern concept of the normal mechanism of urination.⁸⁻¹⁰ It is no longer believed that this mechanism consists of the simple reciprocal contraction of the detrusor muscle and relaxation of the internal sphincter. It is generally held that the mechanism is more complicated, the action of the circular muscle about the internal urethral orifice being overcome by the strong contraction of the trigonal muscle, which pulls the posterior segment of the orifice upward and backward. This action, coupled with the contraction of the detrusor muscle and assisted by the voluntary efforts of the abdominal muscles, effects the passage of urine. This muscle, known as Bell's muscle, is derived from the inner longitudinal muscle layer of the ureters and, spreading laterally to form the prominence known as the interureteric ridge, and downwards and medially toward the urethra, is responsible for the elevation of the trigone above the level of the adjacent portions of the bladder. The anterior fibers of this muscle pass into the posterior urethral wall internal to the circular layer of the internal sphincter. It can readily be seen that its contraction exerts a posterolateral force pulling the posterior segment of the orifice open. In the normal woman the entire trigonal area is fixed and firmly supported by the pubocervical fascia, which adequately resists increases in abdominal pressure. The internal urethral orifice does not come under the influence of any other force than the backward and upward pull of the trigonal muscle.

With the development of a urethrocele consequent on injury to or inadequacy of the supporting tissue, the sphincter mechanism becomes subject to additional forces. Even the slightest increase of intra-abdominal pressure must cause some movement downward and backward of the anterior trigone. This constant tug on the circular muscle of the internal sphincter results in its loss of tone. When sharp increase of intra-abdominal pressure takes place, the anterior trigone herniates through the defect, pulling open the posterior segment of the internal orifice by overcoming the internal sphincter. This accounts for the cystoscopic observations on patients with urethrocele. The resultant incompetence of the internal sphincter accounts for the sudden escape of urine, under the propulsion of the increased intra-abdominal pressure and the normal tone of the detrusor muscle. When intra-abdominal pressure falls, the trigone rises, releasing the internal sphincter, which once more becomes competent. This appears to be the mechanism by which stress incontinence is produced and closely approximates that offered by Taylor and Watt¹¹ in 1917.

It is beyond the scope of this paper to discuss in detail all the surgical procedures that have been employed in the treatment of stress incontinence. While Kelly¹² believed that the fundamental weakness lay in the internal sphincter, and devised an operation, popularly known as the "Kelly stitch" for tightening this muscle, most students of this disorder today believe that the essential weakness lies in the supporting structures about the upper urethra and bladder neck. The success attained by Kelly is attributed to his unconscious inclusion of these tissues in his repair. While some operators¹³ plicate the dilated urethra and bladder neck before approximating the supporting fascia, others^{1, 3} believe that this is unnecessary because the urethra and bladder neck rapidly regain tone and normal dimensions once proper support is attained. Other operators¹⁴ have

stressed the importance of repairing the external sphincter and the advancement of the urethral meatus,¹⁵ although the manner in which the lower third of the urethra can take part in the production of stress incontinence is not clear. Kennedy,⁷ as a result of his recent investigations, advocates a very wide dissection of the urethra and bladder neck. The fascia is freed to its attachment to the pubic bone, from which it is separated, so that the urethra is completely mobilized. The redundant urethra and bladder neck is plicated by interrupted sutures and the supporting fascia closely approximated over this layer by additional interrupted sutures. The external sphincter is approximated in addition. He places great emphasis on the freeing of adhesions between the urethra and the back of the pubis. These he believes are important factors in the incontinence. He has reported excellent results, as has Counsellor,¹⁶ who has followed his technique.

The postoperative results of these procedures have been in the main successful. Few reports, however, equal that of Kelly,¹² who, in 1913, stated that he had been using his procedure for ten to twelve years and had yet to encounter a failure. Most observers who have followed up their cases report a considerable incidence of partially or totally unsuccessful results. Shortly after Kelly's initial article, he reported with Dumm¹⁷ on a series of twenty cases with complete failure in four, or 20 per cent. Watson¹ reported 105 cases with successful results in 65.7 per cent, partial relief in 21.9 per cent, and failure in 12.4 per cent. Furniss,¹⁸ reporting on twenty-one cases, states that of the seventeen patients followed up thirteen were relieved, two were improved, and two were complete failures (12.9 per cent). His failures occurred in patients with an extreme degree of stress incontinence. Kennedy⁷ reporting on twenty-eight cases, states that two failures occurred, an incidence of 7.1 per cent; Bonney,³ while not giving percentages, states that he has failed to achieve surgical cure in some patients. Davies¹⁹ reports 8 per cent failures in a series of 100 cases.

If the facts underlying this condition which have been presented are correct, there are three possible explanations of these failures: first, that the operative procedure has been inadequate; second, that the healing process has been imperfect due to infection or faulty blood supply; and third that the supporting tissues utilized in the repair are so attenuated that they once more give way under the continual assault of intra-abdominal pressure. The first explanation can be discarded since the failures enumerated above have occurred in the hands of experienced operators, most of whom utilized procedures which appear fundamentally correct. Of the second and third explanations, the last appears the most likely since serious infection is rarely seen in operations on the anterior vaginal wall, and in most of the failures, temporary relief is obtained only to be followed by a recurrence of the condition.

If the original supporting structures are so attenuated as to be of no further value, the possibility of transplanting tissue from another source should be considered. This is by no means a new idea.

In 1910, Goebell²⁰ reported on the transplantation of the pyramidalis muscles, attaching their free ends about the neck of the bladder. In 1914 Frangenheim²¹ modified this technique by utilizing, in addition to the pyramidalis, strips of the overlying fascia, and included sometimes part of the rectus muscle. In 1917 Stoeckel²² advised the addition of a vaginal plastic operation to the above procedure. In 1907 Giordano²³ described the use of the transplanted distal end of the gracilis muscle in cases of stress incontinence. In 1911 Squier²⁴ and in 1918 Taussig²⁵ recommended the use of the levator muscles. In 1923 Thompson²⁶ transplanted strips of rectus muscle and fascia downward in front of the pubic bone and sutured them about the lower urethra. Miller²⁷ reported on a somewhat similar procedure in 1932. In 1929, Martius²⁸ described the transplantation of the bulbocavernosus muscle and its surrounding fat in between the urethra and the vagina. In all of these techniques it is to be noted that the substitution of voluntary muscle for a supposedly injured internal sphincter

was considered to be of more importance than the restoration of proper support. This probably accounts for some of the failures which followed the use of these procedures. It is doubtful, moreover, if voluntary muscle will survive in its transplanted condition owing to defects in its nerve and blood supply, and to altered function. One such case has been reoperated in which the voluntary muscle was found to be changed to dense, almost cartilaginous, connective tissue. In 1933 Price²⁹ reported on a case in which he had utilized a strip of fascia lata passed under the urethra by the suprapubic route. The ends of the strips were attached to the rectus muscles on each side; a successful result was attained. Aldridge³⁰ in 1942 reported on the use of transplanted strips obtained from the aponeurosis of the oblique muscles in combination with a plastic operation on the bladder neck and upper urethra. He had obtained complete relief in a patient with stress incontinence who had been operated upon twice before without success. This technique in a somewhat modified form has been utilized by me in a number of cases, four of which have been reported previously.³¹ While caring for these patients, further applications of the same principle have been developed. Experience gained in the use of transplanted abdominal fascia in combination with vaginal plastic operations upon the upper urethra and bladder neck in patients suffering from urethrocele and stress incontinence form the basis for this report.

Technique

The technique utilized in patients with previous operative failures may be described as follows:

Procedure 1.—The patient is put in the dorsal position and the lower abdomen is prepared with merthiolate and draped with towels. The area exposed should include the upper border of the symphysis and both anterior superior iliac spines. A long incision is made with its center about 2 to 3 cm. above the upper border of the symphysis and curving upward on each side of the midline to a point slightly above the anterior superior iliac spines. It extends through skin and fat down to the aponeurosis of the external oblique and the external rectus sheath. The aponeurosis at the bottom of the incision is carefully cleansed of fat and all bleeding is controlled with fine catgut ligatures. The aponeurosis of both the external oblique and internal oblique is incised longitudinally with a scalpel for a distance of 1½ to 2 cm. at the lateral extremity of the skin incision. The inner surface of the internal oblique aponeurosis medial to this incision is freed from the underlying muscle. Beginning at each angle of the incision a strip of the combined aponeurosis is mobilized by means of two parallel incisions extending downward and medially to a point about 1.5 to 2 cm. of the midline. As a rule, some fibers of the internal oblique must be separated from the inner aspect of the strip. A similar strip is then obtained from the opposite side.

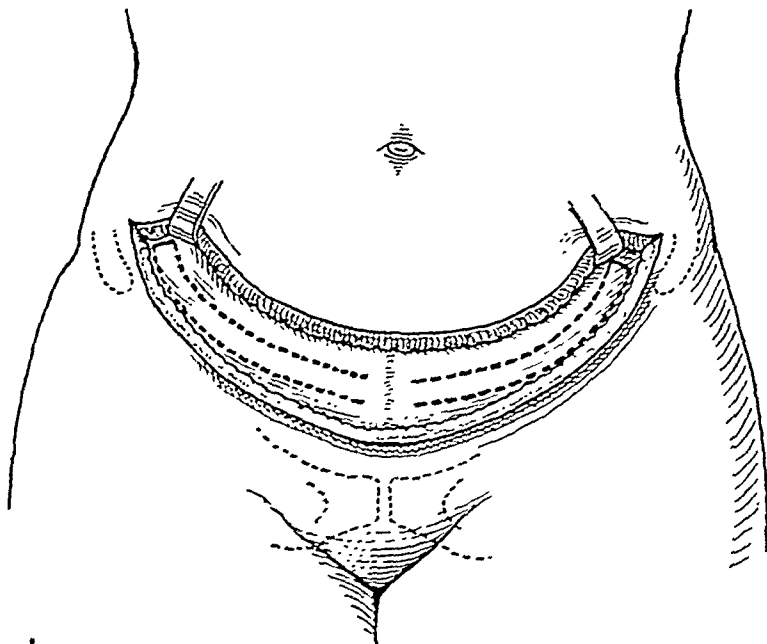


Fig. 1.—Type of abdominal incision utilized in exposing aponeurosis of external oblique and external rectus sheath. The extent of the aponeurotic strips has been outlined.

The attachment of the medial end of each strip is carefully preserved and lies about 1 to 1.5 from the midline (Fig. 1). The defect in the aponeurosis is closed up to the border of the rectus muscle with a running No. 1 chromic catgut suture, care being taken to include both the internal and external layers. Traction sutures are then passed through the tips of the aponeurotic strips and held by small clamps. The strips are then placed in the depth of the incision and the open wound is covered with a sterile towel.

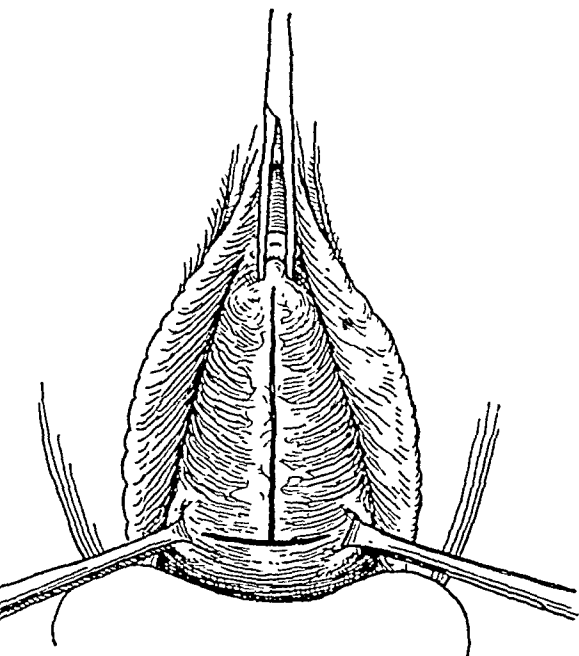


Fig. 2.

Fig. 2.—Inverted T incision over bladder neck and upper urethra. Vaginal wall fixed by means of Allis clamps.

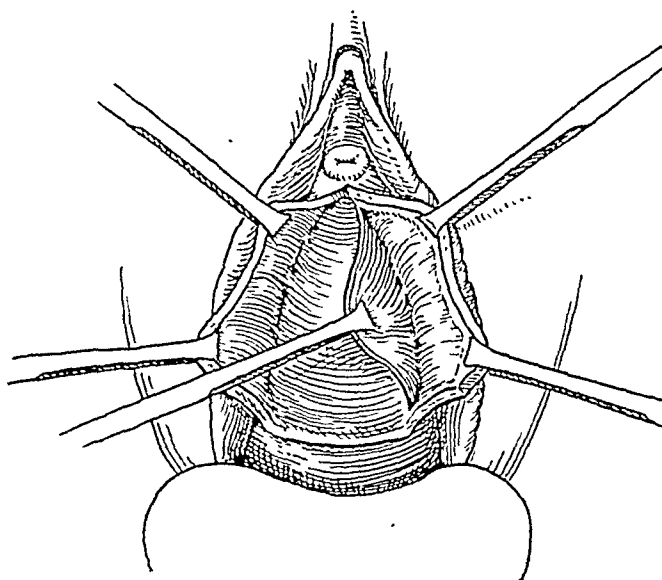


Fig. 3.

Fig. 3.—Vaginal incision completed and plane between pubocervical fascia and vaginal wall defined.

The patient is now put in the lithotomy position, prepared and draped. The labia minora are retracted laterally by stay sutures. A weighted speculum is placed in the vagina exposing the lower anterior vaginal wall. In most of these patients previous operative procedures have resulted in adequate support to the portion of the bladder adjacent to the upper vagina and cervix. As a result of the previous perineorrhaphy the cervix is difficult to draw down or to expose. Since the necessary dissection is mainly about the upper urethra and bladder neck, such exposure is not necessary. The anterior vaginal wall is seized with two Allis clamps, placed as far lateral to the midline as possible, and at as high a level as can be attained. In the midline there is usually the scar of one or more previous operations. Holding the vaginal wall tensely by lateral traction on the clamps, a transverse incision is made with a scalpel through the depth of the vaginal wall (Fig. 2). Scissor dissection at the lateral portions of this incision defines the plane between the bladder and the vaginal wall, following which the scar in the midline can be divided without any risk of injury to the bladder neck and urethra. The vaginal wall is then divided in the midline at right angles to the incision. This last incision should be carried to a point about 1 cm. from the urethral orifice. The plane of the supporting fascia of the bladder neck and upper urethra is then identified, varying amounts of sharp dissection being necessary (Fig. 3). Once found, the plane of separation can usually be followed by blunt dissection with the finger outward and upward to its line of attachment along the inner aspect of the superior pubic ramus. Moderate pressure at this point with the finger results in rupture of the attachment allowing the finger to enter the space of Retzius (Fig. 4). This dissection is carried out on each side. The bladder neck and upper urethra are thus fully mobilized. Considerable bleeding may accompany the latter stages of this dissection due to rupture of veins about the bladder neck. Since the source of bleeding is inaccessible, it is fortunate that it ceases spontaneously after a short interval. The supporting fascia of the upper urethra and bladder neck is then plicated by means of interrupted mattress sutures. If marked relaxation is present, a second layer of such sutures can be added (Fig. 5).

At this point an assistant removes the sterile cover from the abdominal wound. The operator passes a uterine forceps lateral to the bladder neck along the plane of separation of the supporting fascia, through the defect created in the attachment of this fascia into the space of Retzius. On introducing the clamp further, the tip can be felt through rectus muscle by the assistant working above. Slight additional pressure passes the clamp through the body of the muscle. The traction suture attached to the aponeurotic strip on the corresponding side can then be seized and drawn downward in the reverse direction to which the clamp has been passed, drawing after it the strip itself (Fig. 6). This procedure is repeated on the opposite side. The ends of the strips are then approximated by simply tying the traction sutures together, thus forming a sling about the bladder neck (Fig. 7). This sling should be, and usually is, tight enough to pull the bladder neck well up behind the symphysis. It probably cannot be too tight, but if too loose it may fail to produce a good result. If the sling is accessible after the ligatures are tied, a few interrupted sutures may be added to reinforce its point of union. However, satisfactory healing seems to follow even when the retraction of the sling makes this additional procedure impossible. The vaginal mucosa is then closed with interrupted sutures including, when possible, a bite of the underlying tissue to eliminate dead space. As a rule no vaginal mucosa is removed.

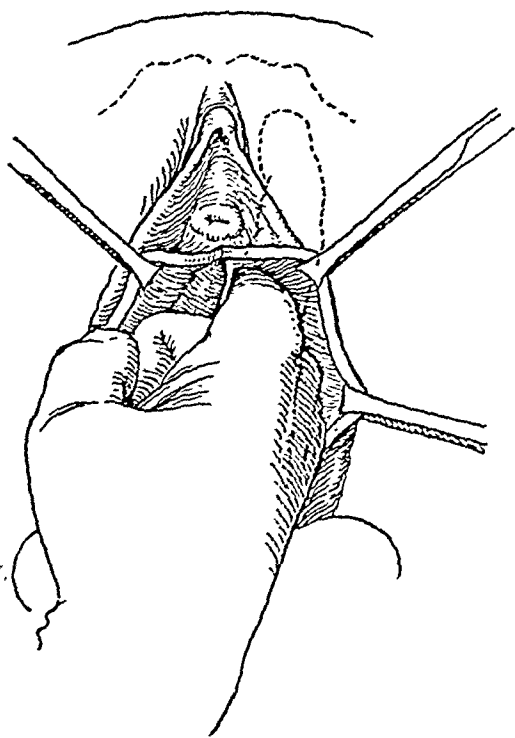


Fig. 4.

Fig. 4.—Plane between pubocervical fascia and vaginal wall followed upward and laterally to pubic attachment. The fascia is ruptured at this point, allowing the finger to enter space of Retzius.

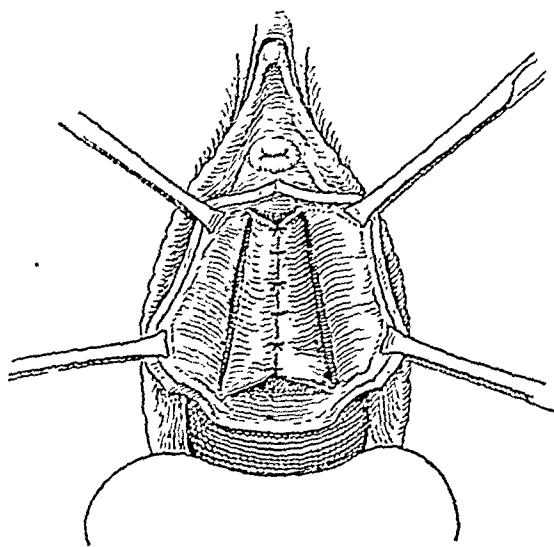


Fig. 5.

Fig. 5.—The pubocervical fascia has been approximated in front of bladder neck and upper urethra by means of mattress sutures.

In the meantime, the abdominal operator is completing the closure of the abdominal incision. The defect in the lateral portion of the external rectus sheath is closed with continuous chromic suture. The fat is closed with a running plain catgut suture. Rubber tissue drains are placed in the depth of the wound and led out of each angle. Four grams of sulfanilamide powder are dusted into the wound because of the likelihood of contamination by organisms introduced by instruments passed upward from the vaginal tract. The skin is then closed with interrupted dermol sutures. The total time necessary for this procedure in recent cases has amounted to about sixty minutes. A large absorbent dressing should be applied to the abdominal wound because of the rather profuse serosanguineous drainage which takes place in the first forty-eight hours. A self-retaining catheter is placed in the bladder.

The important elements in postoperative care are as follows: The abdominal wound should be dressed and the drains removed about forty-eight hours postoperatively. Sulfadiazine, 0.5 Gm., is administered four times a day until the catheter is removed or until the

patient voids, in order to avoid urinary infection. The catheter is removed about the ninth day, spontaneous voiding of urine occurring sometimes immediately, but usually not until a few days later. Catheterization at eight-hour intervals must be carried out during this time. The skin sutures are removed on the ninth day and the patient is allowed up on the eleventh day. So far no infections have been encountered. While all of the cases about to be reported have not been treated in exactly this fashion, this is the routine that has been adopted as a result of experience.

This procedure has been utilized on ten patients who for purposes of classification may be considered in two groups.

In the first group of seven, all of the patients had been subjected to previous plastic operations for the relief of various degrees of relaxation of the pelvic supports. A total of thirteen operations had been performed on them. All of them, in addition, suffered from severe stress incontinence at the time of their initial operation. In all but one of them (Case 3, Group I) satisfactory results had been attained except for the recurrence of urethrocele and the failure to relieve stress incontinence. In some of them this symptom had become increasingly severe. All of the operations had been carried out by competent gynecologic surgeons. Case 3 in this group, a woman who required both a plastic operation and a hysterectomy, should be kept in mind when the patients in Group III are discussed.

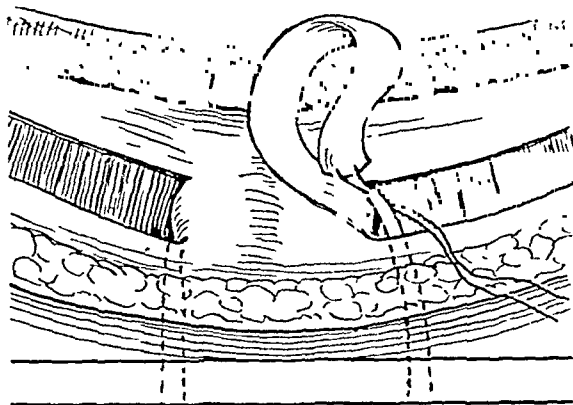


Fig. 6.

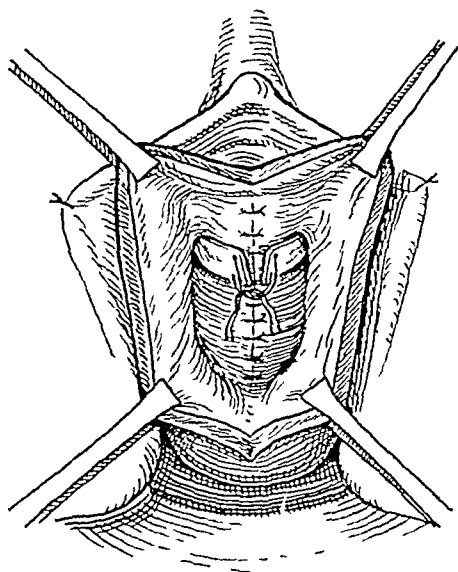


Fig. 7.

Fig. 6.—On the left, uterine forceps has been passed upward between fascia and pubic ramus, through the space of Retzius and the left rectus muscle; it is grasping a traction suture attached to the end of the left aponeurotic strip. On the right, the aponeurotic strip on the corresponding side has been drawn downward by the traction suture in the reverse direction to which the clamp has been passed.

Fig. 7.—The fascial strips are being approximated to form a sling by tying the traction sutures together. This sling should be fairly tight and retracts the bladder neck upward and forward behind the symphysis. Actually, at operation, the bladder neck disappears behind the symphysis so that the sling cannot be seen as depicted by the artist. If accessible, the union of the ends of the strip may be reinforced by interrupted sutures.

TABLE I.4. PATIENTS IN WHOM PREVIOUS SURGICAL EFFORTS HAVE FAILED

PATIENT	CASE NO.	AGE	PARITY	PRIMARY DIAGNOSIS	PREVIOUS SURGERY	RESULT	REMARKS
(1) B. II.	J. V. 8523-43	38	P. iii G. iv	1930. Cystocele. Relaxed perineum. Stress incontinence, dura- tion 7 years	1930. Repair of cystocele— Kelly stitch. Perineorrhaphy. 1935. Repair of cystocele— Kelly stitch. 1940. Repair of bladder neck and upper urethra—Kennedy technique. 1940. Implantation of fascia lata under bladder neck.	Adequate support to bladder adjacent to upper vagina. Bladder neck and upper ure- thra fell away from symphy- sis on straining. Marked stress incontinence	1924. First labor 5 days long. Delivered with low forceps. Beginning of incontinence
(2) B. II.	S. F. 22741-43	42	P. ii G. ii	1942. Cystocele. Relaxed perineum. Stress incontinence, dura- tion 6 years	1942. Repair of cystocele, blad- der neck, and upper urethra —Kennedy technique	Adequate support to bladder adjacent to upper vagina. Bladder neck and upper ure- thra fell away from symphy- sis on straining. Marked stress incontinence	1932-1934. Nine-pound chil- dren. Onset of stress incon- tinence after second delivery
(3) B. II.	S. T. 22794-43	51	P. iii G. v	1938. Cystocele. Relaxed perineum. Large fibromyomas. Stress incontinence, dura- tion 18 months	1942. Repair of cystocele— Kelly stitch. Perineorrhaphy. Supravaginal hysterectomy. 1939. Repair of cystocele, blad- der neck, and upper urethra —Kennedy technique. 1941. Repair of cystocele and interposition of cervical stump	Rapid recurrence of cystocele after each operation. Finally prolapse of vault of vagina and cervical stump. Increas- ing stress incontinence	1926. Left nephrectomy. Stress incontinence appeared in 1940 long after birth of last child in 1919

(4) S. H.	S. W. 638395	55	P. iii G. iv	1941. Slight cystocele. Urethrocele. Stress incontinence, duration 1 year	1912. Repair of supporting fascia about bladder neck and upper urethra	Slight improvement for few weeks after operation. Stress incontinence then returned. Anatomic result good. Urethrocele	Stillbestrol 1 mg. o.d. controlled incontinence. Produced profuse uterine bleeding, requiring curettage
(5) S. H.	M. C. 331479	69	P. iii G. iii	1939. Cystocele. Rectocele. Complete prolapse of uterus. Small fibromyoma. Stress incontinence, duration 3 years	1939. Curettage. Repair of cystocele. Amputation of cervix. Repair of rectocele and perineum	Excellent result as far as support of bladder, uterus and rectum were concerned. Stress incontinence reappeared Jan., 1941. Became progressively worse. Urethrocele	Stress incontinence appeared to be related to development of prolapse after menopause
(6) S. H.	T. M. 759958	50	P. iii G. iv	1941. Cystocele. Relaxed perineum. Stress incontinence, duration 3 years	1941. Repair of cystocele and urethral sphincter. Perineorrhaphy	Adequate support to bladder adjacent to upper vagina. Bladder neck and upper urethra fell away from symphysis on straining. Marked stress incontinence. Urethrocele	
(7) S. H.	R. C. 225197	50	P. vii G. xii	1932. Cystocele. Rectocele. Early pregnancy. Stress incontinence	1932. Vaginal sterilization. Therapeutic abortion. Repair of cystocele, rectocele and perineum. 1933. Repair of fascial supports about bladder neck and upper urethra	Excellent result after first operation except for bladder neck and upper urethra. Stress incontinence continued. Improvement and gradual recurrence of incontinence after second operation. Urethrocele	Incontinence appeared after eleventh pregnancy. Baby born as O.P., spontaneous. No lacerations. Wt. 3350 Gm.

TABLE IB. PATIENTS ON WHOM PREVIOUS SURGICAL EFFORTS HAVE FAILED

PATIENT	CASE NO.	PREOPERATIVE DIAGNOSIS	OPERATION DATA	POSTOPERATIVE COURSE	FOLLOW-UP
(1) B. H.	J. V. 8523 1943	Urethrocele. Stress incontinence	9/ 5/43. D. & C. Procedure 1	Uneventful. No infection. Catheter accidentally removed on 4th day. Not replaced because spontaneous voiding occurred	9/ 6/43. Perfect urinary control. 12/15/43. Slight leakage on going out into cold air. Also when loses temper with children. 10/ 2/44. Condition same. Anatomic result good
(2) B. H.	S. F. 22741 1943	Urethrocele. Stress incontinence	5/15/43. D. & C. Episiotomy. Procedure 1	Uneventful. No infection. No retention catheter used. Voided immediately without trouble	12/ 6/43. Urinary control perfect. 7/16/44. Urinary control perfect. Excellent anatomic result. Feels tug at bladder neck on coughing.
(3) B. H.	S. T. 22794 1943	Urethrocele. Cystocele. Prolapse of cervical stump and vagina Stress incontinence	5/13/43 Extensive plastic excision of cervical stump. Procedure 1	Gradual anuria due to occlusion of right ureter by edema. Relieved by right nephrostomy 5/17/44. Normal urination gradually re-established. No infection	12/ 4/43. Perfect urinary control. 7/16/44. Perfect urinary control. Slight cystocele. Otherwise good anatomic result
(4) S. H.	S. W. 633395	Urethrocele. Stress incontinence	4/ 7/44. D. & C. Procedure 1	Uneventful. No infection. Catheter removed on 10th day. Spontaneous voiding	5/16/44. Perfect urinary control. 9/23/44. Perfect urinary control. Good anatomic result. Slight pain at left angle of abdominal incision. No hernia
(5) S. H.	M. C. 331479	Urethrocele. Stress incontinence	7/18/44. D. & C. Episiotomy. Procedure 1	Uneventful. No infection. Catheter pulled out 2nd day. Spontaneous voiding 8th day	9/23/44. Perfect urinary control. Excellent anatomic result
(6) S. H.	T. M. 759958	Urethrocele. Stress incontinence	10/ 3/44. D. & C. Procedure 1	Uneventful. No infection. Catheter out on 9th day. Spontaneous voiding	11/30/44. Perfect urinary control. Excellent anatomic result
(7) S. H.	R. C. 225197	Urethrocele. Stress incontinence	10/10/44. D. & C. Procedure 1	Fever 103.6° first day. Subsided rapidly. No infection. Catheter out on 9th day. Voided spontaneously	11/30/44. Perfect urinary control. Excellent anatomic result

TABLE II. PATIENTS IN WHOM PROCEDURE 1 WAS USED AS INITIAL OPERATION

PATIENT	CASE NO.	AGE	PARITY	DIAGNOSIS	OPERATION	POSTOPERATIVE COURSE	FOLLOW-UP	REMARKS
(1) S. H.	M. T. 716559	45	P. ii G. iii	Cystocele, urethrocele. Relaxed perineum. Rectocele. Right Bartholin cyst. Stress incontinence—life	8/4/43. D. & C. Plication of fascia beneath bladder and upper urethra. Transplantation of abdominal fascia. Repair of rectocele and perineum. Excision of Bartholin cyst	Fever 102° F., 1st day P.O. Otherwise uneventful. Catheterized until 12th day before spontaneous voiding began. No infection	12/8/43. Perfect control of urination. 9/20/44. Perfect control of urination. Slight weakness left outer angle of abdominal wound	Stress incontinence since childhood. Much worse after pregnancies
(2) S. H.	A. S. 483911	36	P. i G. ii	Urethrocele. Stress incontinence, 8 years, becoming progressively worse	7/28/44. D. & C. Plication of fascia of bladder neck and upper urethra. Transplantation of abdominal fascia	Uneventful. No infection. Catheter removed 12th day. Frequent painful urination for few days	9/23/44. No stress incontinence. Urgency after 3 hours. Anatomic result good	Had normal labor at term. Baby, 3,270 Gm. No lacerations.
(3) S. H.	M. K. 684430	60	P. ii G. ii	Urethrocele. Stress incontinence, 1 year	10/27/44. Plication of fascia of bladder neck and upper urethra. Transplantation of abdominal fascia	Uneventful. No infection. Catheter out 9th day. Unable to void for several days	11/30/44. No stress incontinence. Nocturnal frequency. No evidence of urethrocele	Vaginal hysterectomy and plastic in 1940 for prolapse. Excellent result except for urethrocele

Table IA summarizes the important facts in the past history of the patients in this group.

Table IB summarizes the condition present following the previous surgical failures, the type of operation utilized, the postoperative course, and the follow-up observations in this group.

When this technique was first attempted, it was resolved that it should be confined to patients in whom previous surgical efforts had failed. The apparently successful results attained in the initial cases seemed to warrant its application as a primary procedure in those patients whose stress incontinence seemed to be so marked or whose tissues appeared of such poor quality that the usual repair of the normal fascial supports appeared foredoomed to failure. Those patients, three in number, constitute Group II.

Table II summarizes the important facts in regard to the patients in this group.

While studying these patients, another variety of case was encountered in which a different operative technique was indicated. These patients had multiple complaints and required both plastic and abdominal surgery.

For certain details of the procedure utilized in these patients, indebtedness must be expressed to Meigs,³² who has used a similar operation. It can be described as follows:

Procedure 2.—The dissection about the bladder neck and upper urethra is carried out exactly as has been outlined under the first procedure. However, after the supporting fascia has been plicated by means of interrupted mattress sutures, the vaginal mucosa is closed by interrupted sutures, great care being taken to avoid the inclusion of any of the underlying tissue (Fig. 8). As a result there is left a U-shaped space encompassing the upper urethra and bladder neck, both arms of the U terminating in the space of Retzius. A retention catheter is placed in the bladder.

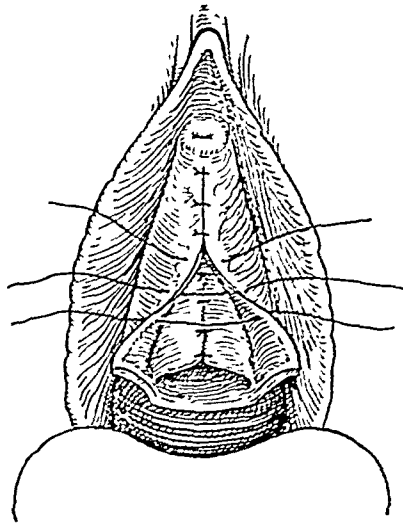


Fig. 8.—Exactly the same type of dissection has been carried out about the upper urethra and bladder neck as has been described in Procedure 1. The vaginal incision is closed, taking care that none of the underlying tissue is included. A U-shaped space is left embracing the bladder neck, the arms of the U terminating in the space of Retzius.

The patient is then put in the dorsal position, prepared with merthiolate and draped. A long, suprapubic midline incision is made, curving to the right of and extending slightly above the umbilicus. The abdominal wall is opened in layers. The medial portion of the external rectus sheath is freed from fat to a width of 1.5 cm. (Fig. 9.) The wound is draped with towels and clips, and the peritoneum opened. After exposing the pelvic organs with a retractor and packing off the intestines into the upper abdomen by means of pads, a complete hysterectomy is carried out, the ovaries and tubes being left or removed as indicated. Before closing the vagina any defect in the pubocervical fascia beneath the upper bladder can be repaired by identifying the stronger, lateral portions of this structure and uniting them by interrupted sutures between the bladder and vagina. The vagina is then closed and all raw surfaces peritonealized in the usual way. The pads and retractors are removed and the peritoneum of the abdominal incision is closed.

A strip, 1 cm. wide, is cut free from the inner margin of the right external rectus sheath, beginning at the upper end of the wound and extending to within 2 cm. of the lower end where its attachment is preserved. This strip should be as long as possible since one

can always get rid of excess tissue. On the other hand, too short a strip is a handicap that cannot be overcome. Great care must be taken in separating the rectus sheath from the underlying muscle at the linea transversae, one of which is always found close to the umbilicus and sometimes another 2 to 3 cm. below it. The muscle is closely attached to the sheath at these points, and unless the separation is carefully made the fascial strip will be weakened enough to break on moderate traction. Having freed the strip, a traction suture is passed through the tip and tied. (Fig. 10.)

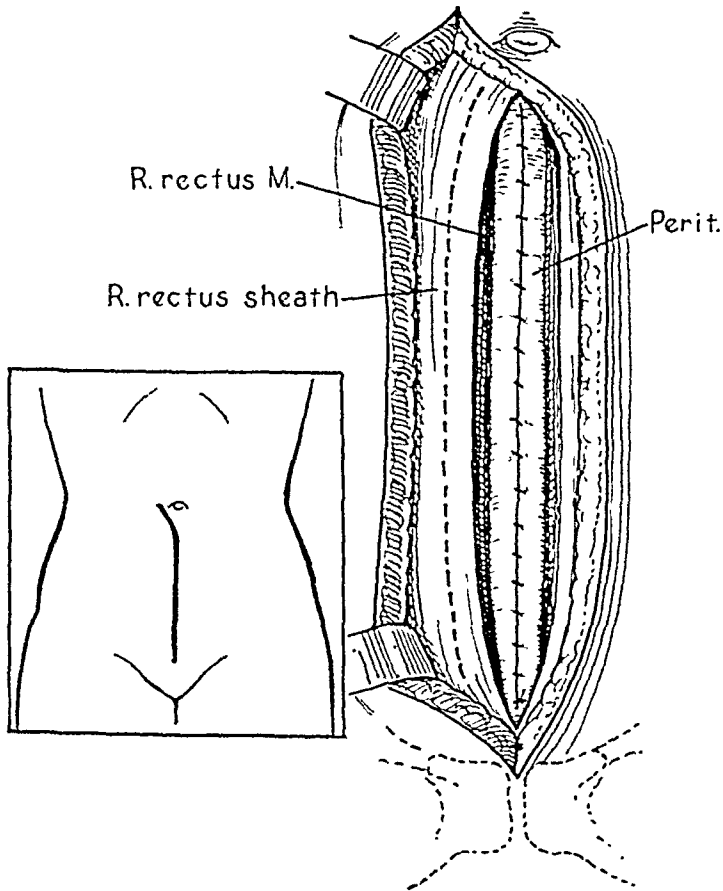


Fig. 9.

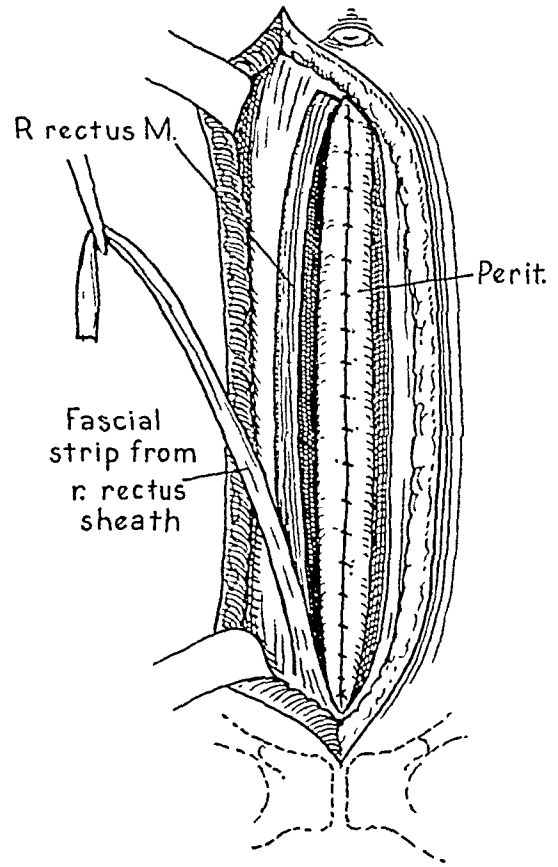


Fig. 10.

Fig. 9.—Inset shows type of incision. Larger drawing shows exposure of external surface of medial portion of right external rectus sheath. The strip to be freed has been outlined. The complete hysterectomy has been carried out and the peritoneum has been closed.

Fig. 10.—The strip has been freed from the median border of the right rectus sheath, leaving the lower end attached.

The anterior wall of the bladder with its pad of fat can now be separated from the posterior aspect of the symphysis. The opening in the prevesical fascia near its attachment to the pubis, made in the dissection of the upper urethra and bladder neck, can be easily identified by an exploring finger. The traction ligature attached to the fascial strip is now threaded on an aneurysm needle, which is passed from right to left, beneath and around the bladder neck, through the U-shaped space left by the previous dissection (Fig. 11). The ligature is seized as it emerges from the left opening of the tunnel, the aneurysm needle is withdrawn, and the attached fascial strip is drawn through the tunnel. The strip is pulled tight enough to bring the bladder neck well up to the back of the symphysis and is then secured by several interrupted No. 1 chromic catgut sutures to the outer aspect of the left external rectus sheath, opposite its attached end on the right side (Fig. 12). Any excess fascia is excised. A cigarette drain is placed in the space of Retzius and 4 Gm. of powdered sulfanilamide are dusted in this area because of the potential danger of infection from the preceding vaginal dissection. The abdominal wall is then closed in layers, care being taken to leave sufficient space at the lower angle to permit free drainage from the retropubic area.

Postoperatively, the patient is given sulfadiazine, 0.5 Gm. four times a day, until the catheter is removed or until spontaneous voiding occurs. The abdominal drain should be gradually shortened but not completely removed until the fourth day, because of the con-

TABLE III. PATIENTS REQUIRING ADDITIONAL ABDOMINAL SURGERY. PROCEDURE 2

PATIENT CASE NO.	AGE	PARITY	CHIEF COMPLAINTS	DIAGNOSIS	OPERATION	POSTOPERATIVE COURSE	FOLLOW-UP
(1) S. H. I. L. 676835	50	P. ii G. ii	Abdominal pain. Abdominal enlargement. Stress incontinence, 6 months	Urethrocele. Slight cystocele. Rectocele. Chronic cervicitis. Fibroids	4/14/44. Procedure 2. Repair of rectocele and perineum. Bilat. salpingo-oophorectomy	Uneventful. Drain out 2nd day. Slight febrile until 9th day. No infection. Catheter out on 6th day. Voided 11th day	7/13/44. Perfect control of urination. Atomic result excellent. 11/15/44. Same findings
(2) S. H. O. M. 742209	48	P. ii G. iv	Menorrhagia. Dysmenorrhea. Stress incontinence	Urethrocele. Cystocele. Slight rectocele. Relaxed perineum. Fibroids	6/ 2/44. Procedure 2. Repair of rectocele and perineum. Bilat. salpingo-oophorectomy	Uneventful. Drain out 3rd day. Slight febrile until 10th day. No infection. Catheter out 9th day. Voided spontaneously 10th day	7/13/44. Perfect control of urination. Atomic result excellent. 11/15/44. Same findings
(3) S. H. E. W. 751519	43	P. iii G. iii	Metrorrhagia. Pelvic pressure. Stress incontinence	Urethrocele. Retroversion. Fibroid. Relaxed perineum	7/14/44. Procedure 2. Perineorrhaphy	Febrile postoperative course. Drain removed 2nd day. Sutures removed 10th day. Small amount of brownish odorless fatty fluid from lower angle. 11th day clean wound disrupted with discharge of large amount of similar fluid. Secondary repair on 18th day. Discharged on 31st day. Catheter out 9th day. Spontaneous voiding on 12th day	9/23/44. No stress incontinence. Has urgency after 3 to 4 hours. Weakness at lower angle of abdominal wound. Hernia?

siderable discharge of liquefied fat and serosanguineous fluid from the space of Retzius. The retention catheter is removed on the ninth day and the abdominal sutures on the tenth day, following which the patient may be allowed out of bed. Spontaneous voiding may occur immediately but sometimes is delayed for a few days. Periodic catheterization is necessary during this time.

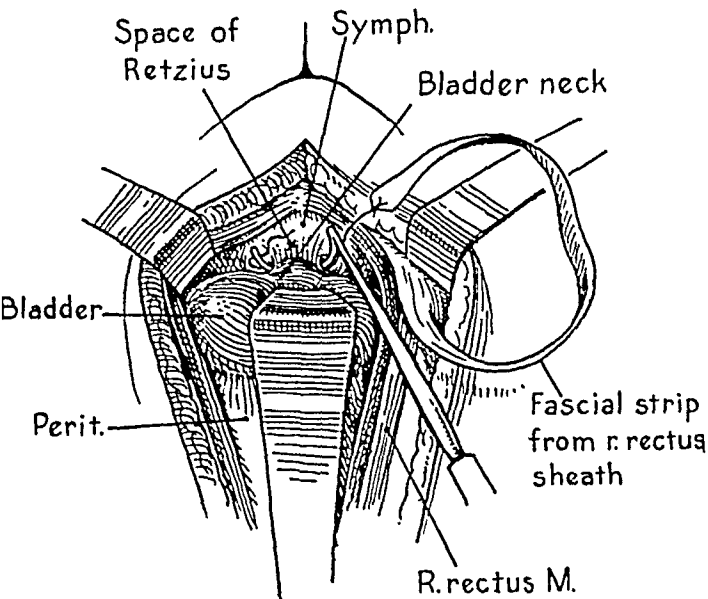


Fig. 11.

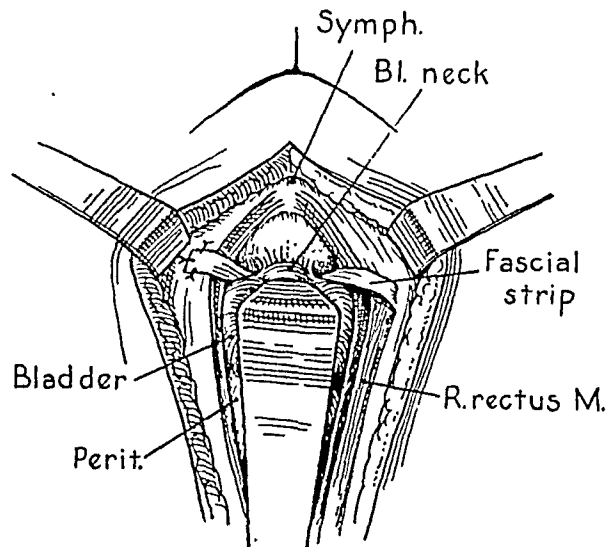


Fig. 12.

Fig. 11.—The bladder has been freed from the posterior aspect of the pubis, and the lateral opening in the pubocervical fascia, made during the vagina dissection, has been identified. A traction suture attached to the end of the fascial strip is being passed about the bladder neck from left to right through the U-shaped space by means of an aneurysm needle.

Fig. 12.—The aneurysm needle has been withdrawn and the fascial strip has been drawn through the space by means of the traction suture. It has been attached to the outer aspect of the left external rectus sheath by several interrupted sutures. The sling thus formed should be tight enough to hold the bladder neck behind the symphysis. Excess fascia may be excised.

This alternative technique has been carried out as a primary procedure on three patients. All of them, in addition to showing various degrees of pelvic relaxation and associated stress incontinence, were found to have uterine fibroids, which produced menorrhagia, metrorrhagia, or pressure symptoms.

Table III shows the important clinical facts in regard to this third group of patients.

Case 3 deserves special mention because of the postoperative course. It is believed that an insufficient exit was left in the lower rectus sheath and that the drain was removed too early. The broken-down fat and serum then dissected upward between the rectus muscles, resulting in the disruption of a wound which showed no gross evidence of infection. On this experience is based some of the precautions mentioned in the description of the operative technique and postoperative care. It is believed that this complication can be avoided in the future by proper attention to adequate drainage of the space of Retzius.

Thirteen patients, suffering from stress incontinence, have been operated upon. In all of them the normal supporting tissues of the upper urethra and bladder neck have been dissected free and plicated beneath these structures. This repair has been reinforced by the formation of a fascial sling obtained from the aponeurosis of the abdominal wall by one of the two procedures which have been described. Although ten of the thirteen patients (Groups I and II) represent cases in which perfect results would seem unlikely if more orthodox procedures had been employed, failure to relieve stress incontinence has yet to be observed. The value of the procedure to patients in Group III cannot be so strongly emphasized, since it is possible that equally good results might have been attained by the usual form of vaginal plastic followed by supravaginal hysterectomy. That the latter type of procedure is open to failure is shown by Patient 3, Group I, whose initial operation was of this variety. The permanence of the results obtained cannot be fully judged as yet. Only eighteen months have elapsed since the first patient was operated on by this type of procedure. It is felt that at least five years with freedom from stress incontinence must elapse before a permanent cure can be assumed.

Some explanation must be offered for the effectiveness of this operation. It is believed the initial plastic repair of the residue of the normal supports of the upper urethra and bladder is of great importance, since, in performing it, these structures are mobilized from the adjacent vagina and from the pubic rami and elevated to a certain extent behind the symphysis. The formation of the fascial sling further elevates and fixes the bladder neck behind the symphysis, and, in healing, reinforces the vulnerable area in the anterior portion of the pubocervical fascia, at which recurrence of the urethrocele can take place. It has been suggested that the sling may cause a kink or stricture of the upper urethra but no evidence of the latter is present on catheterization or cystoscopy of these patients after their operations. In all but one, the voiding mechanism appears to be perfectly normal. In the one exception, Case I, Group II, urination takes place in two installments, separated by an interval of a few seconds. Aldridge,³⁰ in his original report, postulated that tightening of the abdominal muscles as on coughing and sneezing pulled the sling upward, compressing the bladder neck and thus preventing incontinence. This explanation predicates a rather marked degree of mobility in the sling once full healing has taken place, a condition which would seem most unlikely. In fact, only one of the patients reported above states that she has any sensation in the region of the bladder on coughing or straining. Patient 2, Group I, however, states that she is aware of a distinct tug in the region of the bladder neck. It seems more likely that the chief value of the fascial sling is twofold. In the immediate post-operative period, it fixes the bladder neck at a high level; its attached extremities preserve the vitality of the tissue because of their circulatory connections. Completely detached strips of fascia lata transplanted under the bladder neck, a procedure attempted by the late Frank Sovak and myself, uniformly undergo necrosis and slough out (see Case 1, Group I, Table IA, Operation No. 4). The unavoidable secondary infection in vaginal plastic operations may be a factor in the destruction of completely transplanted tissue. The value of the fascial sling in the remote postoperative period lies in the fact that when it is fully healed and incorporated in the undersurface of the anterior pubocervical fascia, the resultant support to the anterior trigone is so strong that it is impossible for the urethrocele to recur. If this explanation is true, the value of the abdominal attachment of the sling is negligible in so far as its traction mechanism is concerned. It is believed that it could be divided from its attachment to the rectus sheath without impairing the control of urination in a patient who suffered from symptoms in the postoperative period attributable to tightness of the sling.

Summary and Conclusions

1. The anatomic basis for urethrocele and its associated symptom, stress incontinence, has been reviewed and discussed, together with the etiological factors which produce this condition.

2. The common type of surgical repair has been reviewed, calling attention to the incidence of failure attendant upon it. Failure appears to be related to the attenuated character of the residual supporting tissue.

3. The use of transplanted tissues has been reviewed, and attention drawn to the faulty concept when voluntary muscle is used.

4. Two methods, utilizing strips of abdominal aponeurosis in addition to plastic repair of the supports of the upper urethra and bladder neck, have been described.

5. Thirteen cases are reported in which these procedures have been used. Close follow-up has so far not revealed a recurrent urethrocele or the reappearance of stress incontinence.

6. The basis for the results attained by these procedures has been discussed:

7. It is believed that these procedures are especially adapted to patients in whom the repair of the normal supports has failed to achieve a good result. In addition, it is believed that, by careful selection, these procedures may be applied as a primary operation in certain cases.

References

1. Watson, B. P.: *Brit. M. J.* 2: 566, 1924.
2. Berkeley, C., and Bonney, V.: *Textbook of Gynecological Surgery*, ed. 4, New York, 1943, Paul B. Hoeber, Inc., p. 535.
3. Bonney, V.: *J. Obst. & Gynec. Brit. Emp.* 30: 358, 1923.
4. Salmon, U. J., Walter, R. I., and Geist, S. H.: *Am. J. Obst. & Gynec.* 42: 845, 1941.
5. Kennedy, W. T.: *AM. J. OBST. & GYNEC.* 33: 19, 1937.
6. Kennedy, W. T.: *AM. J. OBST. & GYNEC.* 34: 576, 1937.
7. Kennedy, W. T.: *AM. J. OBST. & GYNEC.* 41: 16, 1941.
8. Young, H. H., and Wesson, M. B.: *Arch. Surg.* 3: 1, 1921.
9. Young, H. H., and Machit, D.: *J. Pharmacol. & Exper. Therap.* 22: 329, 1923.
10. MacAlpine, J. B.: *Proc. Roy. Soc. Med.* 28: 39, 1934.
11. Taylor, H. C., and Watt, C. H.: *Surg., Gynec. & Obst.* 24: 296, 1917.
12. Kelly, H. A.: *Urol. & Cutan. Rev.* 17: 291, 1913.
13. Johnson, H. W.: *Surg., Gynec. & Obst.* 53: 97, 1931.
14. Young, E. L.: *J. A. M. A.* 79: 1753, 1922.
15. Fracow, S. G.: *AM. J. OBST. & GYNEC.* 41: 1051, 1941.
16. Counseller, V. S.: *AM. J. OBST. & GYNEC.* 45: 479, 1943.
17. Kelly, H. A., and Dumm, W. M.: *Surg., Gynec. & Obst.* 18: 444, 1914.
18. Furniss, H. D.: *AM. J. OBST. & GYNEC.* 8: 195, 1924.
19. Davies, J. W.: *J. Urol.* 48: 536, 1942.
20. Goebell, R.: *Ztschr. f. gynäk. Urol.* 2: 187, 1910.
21. Frangenheim, P.: *Verhandl. d. deutsch. Gesellsch. f. Chir.* 43: 149, 1914.
22. Stoeckel, W.: *Zentralbl. f. Gynäk.* 41: 11, 1917.
23. Giordano, D.: *Assoc. franc. de Chirurg., Congr. de Chir., Paris*, 20: 506, 1907.
24. Squier, J. B.: *Med. Rec.* 79: 868, 1911.
25. Taussig, F. J.: *Am. J. Obst.* 77: 881, 1918.
26. Thompson, R.: *Brit. J. Child. Dis.* 20: 146, 1923.
27. Miller, U.: *J. A. M. A.* 98: 628, 1932.
28. Martius, H.: *Chirurg.* 1: 769, 1929.
29. Price, P. B.: *Arch. Surg.* 28: 1043, 1933.
30. Aldridge, A. H.: *AM. J. OBST. & GYNEC.* 44: 398, 1942.
31. Studdiford, W. E.: *AM. J. OBST. & GYNEC.* 47: 764, 1944.
32. Meigs, J. V.: *AM. J. OBST. & GYNEC.* 47: 774, 1944.

768 PARK AVENUE

TREATMENT OF HYPOOVARIANISM BY THE SEQUENTIAL AND CYCLIC ADMINISTRATION OF EQUINE AND CHORIONIC GONADOTROPINS—SO-CALLED ONE-TWO CYCLIC GONADOTROPIC THERAPY

Summary of Five Years' Results*

E. C. HAMBLÉN, M.D., AND C. D. DAVIS, M.D., DURHAM, N. C.

*(From the Endocrine Division of the Department of Obstetrics and Gynecology,
Duke University School of Medicine and Duke Hospital)*

THE first series of so-called one-two cyclic gonadotropic therapy was administered, during the latter part of October and the first part of November of 1939, to a patient with ovarian sterility, who became pregnant during the treatment. Details of this therapeutic schedule and the history of this patient were reported by one of us (E. C. H.) about the middle of November, 1939, at the annual meeting of the Southern Medical Association in Memphis, Tennessee. At this time, it was stated that the sequential and cyclic employment of equine and chorionic gonadotropins warranted further and more intensive study. Subsequently, our group gave reports upon results of this therapeutic

*This study was aided by grants to one of us (E. C. H.) as follows: From the Research Council of Duke University; from Ayerst, McKenna & Harrison, Ltd., Montreal, Canada; from Schering Corporation, Bloomfield, N. J.; from The Upjohn Company, Kalamazoo, Mich.; and from the National Committee on Maternal Health, New York, N. Y. Preparations of equine gonadotropin included Anteron (Schering Corporation) and Gonadogen (Upjohn Company); those of chorionic gonadotropin included APL (Ayerst, McKenna & Harrison) and chorionic gonadotropin (Upjohn Company).

schedule in the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY of October, 1940,¹ and of March, 1941.² Although there have been numerous additional references to this method of treatment in reports by our group, there has been no over-all summary of results since September, 1941.³ Accordingly, this communication brings up to date our results.

Our clinical studies with gonadotropins began in 1930. In 1932⁴ and 1933⁵ reports upon the studies of ovaries of women treated preoperatively with chorionic gonadotropin indicated the nonoccurrence of follicle stimulation, ovulation, or corpus luteum elaboration. Similar observations upon larger groups of patients later were reported.^{6, 7} Clinical applications of gonadotropic therapy had yielded scanty evidence of success as late as 1939.⁸

The studies of Davis and Koff in 1938⁹ of ovarian responses of women treated preoperatively with equine gonadotropin demonstrated the follicle-stimulating activity of this gonadotropin and engendered hopes of its effective application to the therapy of hypoovarianism. To permit effective therapy of hypofunctioning ovaries, a gonadotropin should evoke, in sequence, follicle stimulation, ovulation, and corpus luteum development, and these phenomena should be of physiologic order compatible with fertility and conception. Save for an occasional enthusiastic report, the consensus soon was manifest that equine gonadotropin was failing to warrant earlier therapeutic hopes.

Our group¹⁰ showed that the cyclic administration of equine gonadotropin, in amounts judged to be adequate, during the follicular phase of the cycle—that is, from the fifth to the fourteenth days of the cycle—failed to result in progestational bleeding (as judged by endometrial biopsy studies) or in pregnancy in women who bled from interval or estrogenic endometriums, in many of whom ovarian sterility constituted a major problem.

On the other hand, we showed³ that, when a similar group of women (with regard to ovarian status and number) was treated with the same equine gonadotropin but, in addition, was given injections of chorionic gonadotropin from the fifteenth through the twenty-fourth days of their cycles, there occurred a substantial number of progestational endometriums and a number of pregnancies. This therapeutic schedule was named one-two cyclic gonadotropic therapy.

This present communication will show that our early impressions of the effectiveness of this therapy have not been altered significantly by the passage of time or by the accumulation of more data.

Selection of Patients

A total of 116 patients with hypofunctioning ovaries was studied.

The patients fell into four clinical categories: (1) those with deficient sexual maturation whose menarches had not occurred, seven patients; (2) those with infrequent and/or scanty bleeding, fourteen patients; (3) those with prolonged and/or excessive bleeding, thirty-one patients; and (4) those with ovarian sterility, sixty-four patients.

These groups embraced the thirty-one patients whose responses were reported in September, 1941.³ The records of these patients were restudied and re-evaluated.

1. *Patients With Deficient Sexual Maturation Whose Menarches Had Not Occurred.*—All possessed striking hypoenestrogenism. In none was a definite diagnosis of hypopituitarism made. Accordingly, the likelihood of an intrinsically ovarian etiology existed in all. The endocrine state of these patients was not relatable to organic or constitutional disease. Hypothyroidism, as an etiological factor, was eliminated by clinical studies, basal metabolic rates and by preliminary treatment with desiccated thyroid gland of those patients in whom there was some evidence of hypothyroidism.

2. *Patients With Infrequent and/or Scanty Bleeding.*—Upon the basis of endometrial biopsies secured at the onsets of episodes of uterine bleeding, all of these patients were

judged to have anovulatory ovarian failure—that is, they bled from interval or estrogenic endometriums. There was no evidence of hypoenestrogenism.

No more definite statements of the etiology of the ovarian failure for this group of patients were possible than for the first group.

3. *Patients With Prolonged and/or Excessive Bleeding.*—In common with the patients of the second group, these patients were characterized by anovulatory ovarian failure without hypoenestrogenism—that is, all bled from estrogenic or interval endometriums.

Similar to the patients of the first and second groups, no definite diagnoses of the etiology of the ovarian failure were possible; however, constitutional and organic gynecologic factors were excluded.

4. *Patients With Ovarian Sterility.*—This group of patients comprised two subgroups: (a) Patients whose bleeding was associated with interval or estrogenic endometriums, that is, who had anovulatory failure, fourteen in number; and (b) patients whose bleeding occurred from immature progestational endometriums, fifty in number.

We assumed that bleeding from immature progestational endometriums by patients of the second subgroup was significant of endocrine deficiency since no other demonstrable causes of sterility were found in careful diagnostic surveys of these wives and their husbands. We considered two likely mechanisms: (1) ovulations might have occurred and, yet, the immature progestational endometriums might have prevented nidation of any fertilized ova, that is, the existence of hypoprogenitism without anovulatory ovarian failure; and (2) ovulations might not have occurred and, instead, ova were imprisoned in follicles the granulosa of which subsequently became luteinized providing low progestin stimulation of the endometrium, that is, the existence of anovulatory ovarian failure and hypoprogenitism. Acceptance of the latter of these two mechanisms justified the application of one-two cyclic gonadotropic therapy.

No more definite causes for the two grades of ovarian failure of this group of patients were ascribable than for that of the patients of the third group.

All of the patients of the fourth group experienced cyclic and essentially normal bleeding with regard to duration and amount. Therefore, they stand in striking contrast to the patients of the second and third groups.

Method of Study

The clinical studies of all of the patients embraced endocrine and gynecologic surveys, determinations of basal metabolic rates, and roentgenograms of the sella turcica. Roentgenologic estimations of osseous age were made in those patients with deficient sexual maturation and those 20 years or less of age. Endometrial biopsies were done at the onset of episodes of bleeding, prior to, during, and frequently after therapy. Because of the hypoenestrogenism of the patients of the first group, initial biopsies were omitted. At least two consecutive episodes of bleeding were biopsied, if possible, prior to treatment of the patients of the second, third, and fourth groups. This seemed advisable lest chance variations might be classed as ovarian habits of a patient.

All biopsy material, after fixation, mounting, and staining, was studied and classified by one of us (E.C.H.). This practice has been followed in previous studies and, thereby, has permitted a uniformity and continuity of interpretation of endometrial responses.

Special methods of study and of handling of the patients of the four groups are detailed.

1. *Patients With Deficient Sexual Maturation Whose Menarches Had Not Occurred.*—Urinary levels of gonadotropins and 17-ketosteroids were established in some of these patients. (These data will be reported in subsequent communications.) Studies of vaginal smears, stained by Mack's iodine vapor method,¹¹ were made prior to and during therapy; the results were in essential agreement with the other data to be reported.

Cyclic estrogen therapy was given to produce sexual maturation and to initiate withdrawal bleeding. Cyclic estrogen-progesterone therapy then followed, and endometrial biopsies were taken at the onsets of subsequent bleeding episodes. When an endometrial biopsy showed a progestational endometrium, treatment was discontinued and, subsequently, when bleeding followed twenty-eight to thirty days of no treatment or even when bleeding did not recur after this length of time, an endometrial biopsy was taken as a salvage test. The purpose of the salvage test was to exclude the recovery of normal ovarian function during the antecedent cyclic steroid therapy. When a progestational endometrium was found on salvage test, the patient was not given gonadotropic therapy.

The purpose of the cyclic estrogen-progesterone therapy is to prove the endometrium capable of responding to progestin. This is essential to the use of the endometrium as an indicator of the effectiveness of gonadotropic therapy. If an endometrium is incapable of responding to progestin therapy, it will fail to respond to any progestin which is caused to be elaborated by the ovaries by gonadotropic therapy.

Following a negative salvage test, one-two cyclic gonadotropic therapy was given and endometrial biopsies were taken, either at the onset of bleeding following this therapy or within seven days after the conclusion of therapy if no bleeding occurred. A positive response was the finding of a progestational endometrium.

Previous clinical experience had not indicated that we should expect regulation of bleeding from gonadotropic therapy. The present studies agreed.

2. *Patients With Infrequent and/or Scanty Bleeding.*—The method of study of these patients was essentially that of the first group. These patients did not require cyclic estrogen therapy for sexual maturation and, accordingly, were given only cyclic estrogen-progesterone therapy. This served both to regulate their bleeding and as a test of endometrial receptivity. The salvage test after this therapy was done and gonadotropic therapy was evaluated as in patients of the first group.

3. *Patients With Prolonged and/or Excessive Uterine Bleeding.*—The majority of these patients was seen during episodes of prolonged and/or excessive uterine bleeding. These patients required, as the first measure, control of the excessive and/or prolonged flowing. This was accomplished generally by the hemostatic use of estrogen. Once hemostasis was obtained, cyclic estrogen therapy was given to regulate the cycle and to secure withdrawal bleeding of essentially normal duration and amount.

Endometrial evaluations of these patients, which were used as base lines for gonadotropic therapy, were made after cycle regulation had been secured and after steroid therapy was discontinued.

Cyclic estrogen-progesterone therapy was used as a test for endometrial responsiveness and a salvage test was done as in the patients of the first and second groups. Patients who gave a negative salvage test were treated with one-two cyclic gonadotropic therapy and the results of this therapy were evaluated as previously described.

4a. *Patients With Ovarian Sterility Characterized With Estrogenic Bleeding.*—These patients were handled identically with those of the second and third groups as to a test of endometrial receptivity with cyclic estrogen-progesterone therapy, salvage test, and one-two cyclic gonadotropic therapy.

4b. *Patients With Presumed Sterility and Immature Progestational Bleeding.*—These patients did not require a test of endometrial receptivity since they bled from progestational endometria. A salvage test was unnecessary for the same reason. One-two cyclic gonadotropic therapy was given and its results were tested as in the other groups.

In both sterility groups the occurrence of pregnancy during therapy was regarded as a positive response.

Therapeutic Schedules

The therapeutic schedules used in these studies are summarized.

Hemostasis.—The average daily dosage of estrogen employed for hemostasis is represented by 6 mg. of diethylstilbestrol or its equivalent in estrone sulfate. Not all patients were treated with oral estrogens during the earlier years of the study. A comparable amount of estrogen by injection was used. After hemostasis was obtained, estrogen therapy at the same dosage level was continued daily for another twenty days.

Cyclic Estrogen Therapy.—Cyclic estrogen therapy was begun on the third to fifth day of the cycle and continued for twenty days, when it was withdrawn, or earlier if bleeding occurred. It was resumed on the third to the fifth day of the cycle. This therapy was usually kept up two or three months.

The usual daily dosage is represented by 3 mg. of diethylstilbestrol or its equivalent in estrone sulfate. The majority of patients were treated orally; however, in earlier years, some received injections.

Cyclic Estrogen-Progesterone Therapy.—This therapy was started on the fifth day of the cycle. Estrogen was given orally and in daily dosages represented by 3 mg. of diethylstilbestrol, or the equivalent in estrone sulfate, for twenty days. During the last ten days of this treatment, the patient received orally and daily 60 mg. of anhydrohydroxy-progesterone. Not all patients received oral therapy. Some received similar amounts of estrogen and progesterone by injection in the earlier years of the study.

One-Two Cyclic Gonadotropic Therapy.—Prior to initiating one-two cyclic gonadotropic therapy, all patients were skin tested with the equine gonadotropin preparation to ascertain possible allergy. Skin tests were repeated before each projected series of therapy. Patients with definite allergy were not treated.

Gonadotropins were given intramuscularly and daily. Therapy was initiated on the fifth day of the cycle. From the fifth through the fourteenth days of the cycle, patients received intramuscularly and daily 400 international units of equine gonadotropin. From the fifteenth through the twenty-fourth days of the cycle, patients received intramuscularly and daily 500 international units of chorionic gonadotropin. When bleeding occurred before treatment was completed, injections were discontinued.

As a rule, and out of respect for possible antibody or antihormonal phenomena, series of one-two cyclic gonadotropic therapy were not given in sequence but, instead, several months were allowed to elapse between any two series of therapy.

Clinical Data and Results

1. *Patients With Deficient Sexual Maturation Whose Menarches Had Not Occurred.*—The ages of these seven patients ranged from 16 to 26 years. The average age was 19.5 years.

These seven patients received eleven series of one-two cyclic gonadotropic therapy. The results of ten of these eleven series of therapy were sampled by endometrial biopsies. Ninety per cent of the endometrial biopsies, or nine biopsies, yielded estrogenic endometria: eight hypoestrogenic and one quite adequately proliferated. Ten per cent, or one biopsy, showed an immature progestational endometrium.

The patient from whom the immature progestational endometrium was obtained gave this response on the third series of gonadotropic therapy. The other two series of therapy given this patient had yielded hypoestrogenic endometria.

Five of the seven patients bled following gonadotropic therapy. One of the five patients received three series of gonadotropic therapy and bled after one series but did not bleed after the other two series. None of the patients had subsequent bleeding except when they were given cyclic steroid therapy.

2. *Patients With Infrequent and/or Scanty Uterine Bleeding.*—The ages of these fourteen patients ranged from 17 to 35 years, thus placing all of them in the late adolescent or reproductive epochs. The average age was 25 years.

The menarcheal ages of these patients ranged from 10 to 17 years with an average of 13.3 years.

Seven were single and seven were married. Of the seven married patients, four were nulliparous and the others had had, respectively, one abortion, one term delivery, and two term deliveries.

The character of their bleeding histories varied. Seven reported last episodes of bleeding ranging from four years to six months. Five patients had intervals ranging from three to six months. Two patients had intervals which ranged from two to three months in length. The bleeding in many of these patients was scanty in amount and short in duration.

Twelve of the patients bled from well-developed estrogenic endometria and two bled from hypoestrogenic endometria.

The fourteen patients received twenty-two series of one-two cyclic gonadotropic therapy. Seventeen of these series of therapy which were given thirteen of the fourteen patients were sampled by endometrial biopsies. Four patients (30.8 per cent) yielded progestational endometria following treatment: three patients, immature progestational endometria, and one patient, a full-blown progestational endometrium. The other nine patients yielded estrogenic endometria: six normal estrogenic endometria and three hypoestrogenic endometria.

In none of the patients were the duration and amount of bleeding affected or the irregularity of the cycle improved.

One of the patients who gave a positive response had a follow-up biopsy at the onset of bleeding one month following discontinuation of treatment; this biopsy indicated a full-blown progestational endometrium.

3. *Patients With Prolonged and/or Excessive Uterine Bleeding.*—The ages of these thirty-one patients ranged from 14 to 31 years, an average age of 23.5 years. Accordingly, all of these patients were in the adolescent or the early reproductive epochs.

Menarcheal ages of these patients varied from 11 to 16 years, an average age of 13 years.

Eighteen of these patients were single and thirteen were married. Of the thirteen married patients, eight were nulliparous, three had had a pregnancy which resulted in a term delivery, one had had four abortions, and a term pregnancy, and one had had an abortion.

The character of the bleeding history of these patients varied. When first seen, twenty-two patients had had continuous bleeding ranging from one month to four years. Nine patients were having various grades of prolonged and/or profuse bleeding, six being cyclic and three being infrequent. The severity of the hemorrhage of these patients is indicated by their hemoglobin readings which ranged from 10 to 100 per cent with an average of 62 per cent. Sixteen patients had hemoglobins less than 60 per cent.

All patients, prior to therapy, bled from estrogenic endometriums.

A total of fifty-three series of one-two cyclic gonadotropic therapy was given to the thirty-one patients. Fourteen, or 45.2 per cent, yielded progestational endometriums. One patient gave a positive response during each of two series of treatment. There were six full-blown progestational and nine immature progestational endometriums encountered during therapy. A total of fifteen series of therapy, therefore, terminated in progestational bleeding, whereas thirty-two series of therapy terminated in estrogenic bleeding; the results of six series were not sampled by biopsy.

Follow-up biopsies, which were done usually at the first episodes of bleeding which terminated no treatment cycles, subsequent to gonadotropic therapy, were done twenty-three times in nineteen patients. Nine of the nineteen patients yielded progestational endometriums: full-blown progestational endometriums in two patients and immature progestational endometriums in seven patients. Seven of these nine follow-up progestational responses occurred in patients who had had progestational endometriums during gonadotropic therapy, whereas two occurred in patients who had yielded estrogenic endometriums during therapy.

Accordingly, 45.2 per cent of the patients yielded progestational responses concurrent with gonadotropic therapy, whereas 47.4 per cent of the patients, followed up after discontinuation of therapy, yielded progestational responses one month or more after the treatment ended. When several follow-up biopsies were done after therapy, it was found generally that the progestational response gave way to an estrogenic response on the second biopsy.

4a. *Patients With Ovarian Sterility Associated With Estrogenic Bleeding.*—The ages of these fourteen patients ranged from 24 to 35 years. The average age was 29 years.

Menarcheal ages of these patients ranged from 11 to 14 years. The average age was 12.6 years.

Ten of these patients were nulliparous. Two had had a term delivery, and two an abortion.

The duration of the sterility of these patients ranged from one to ten years. The average duration was 3.4 years.

All pretreatment biopsies on these patients yielded normally proliferated estrogenic endometriums.

These fourteen patients received twenty-one series of one-two cyclic gonadotropic therapy, an average of 1.5 series per patient.

The endometrial responses of seven of these patients were not sampled by biopsy; however, two of these patients became pregnant during the first series of treatment and one during the second series of treatment. The occurrence of pregnancy in these three patients, therefore, is assumed to indicate positive ovarian responses.

The endometrial responses were sampled by biopsy in the other seven patients. Four of these patients yielded progestational responses, three yielding immature progestational endometriums and the other a decidua-like endometrium. The subsequent course of this last patient indicated that implantational bleeding had occasioned biopsy rather than menstrual bleeding. The pregnancy of this patient, however, progressed normally.

Accordingly, gonadotropic therapy of these fourteen patients resulted in four pregnancies, whereas three other patients gave progestational responses. Thus, the incidence of positive response was 50 per cent and the incidence of pregnancy was 28.6 per cent. Two of the pregnancies resulted in term deliveries of normal children, one is nearing term, and the other is yet in an early stage.

4a. *Patients With Ovarian Sterility Associated With Bleeding From Immature Progestational Endometriums.*—The ages of these fifty patients ranged from 21 to 41 years; twenty-four patients were between 21 and 29 years of age; twenty-three were between 30 and 39 years of age; and three patients were between 40 and 41 years of age.

Menarcheal ages of these patients ranged from 11 to 17 years, the average being 12.9 years.

Thirty-seven of these patients were nulliparous. Five had had a term delivery, five an abortion, two had had two abortions and one four abortions.

The duration of the sterility of these patients ranged from one to ten years, an average sterility of 3.08 years.

A total of ninety-one pretreatment biopsies was done upon the fifty patients, with an incidence of 1.82 biopsies per patient. Distribution of the biopsy findings was: inadequate tissue for diagnosis, three; estrogenic endometriums, five; full-blown progestational endometriums, nine; and immature progestational endometriums, seventy-four. All of the patients, however, presented immature progestational endometriums as a predominant bleeding pattern.

These fifty patients received ninety-six series of one-two cyclic gonadotropic therapy, an average of 1.96 series per patient.

No endometrial biopsies were done during eighty-one cycles or after 84.3 per cent of the series of treatment. The criterion for responses in these was the occurrence of pregnancy.

Of the fifteen cycles of therapy, the results of which were sampled by biopsy, eight cycles terminated in bleeding from immature progestational endometriums, six cycles in bleeding from full-blown progestational endometriums, and one cycle could not be evaluated because of insufficient tissue. These fifteen cycles were distributed among fourteen of the fifty patients. Of these fourteen patients, three became pregnant. All of these patients yielded full-blown progestational endometriums following therapy. One pregnancy occurred the month following a second series of treatment. The second pregnancy occurred during a second series of therapy. The third pregnancy occurred during the first series of treatment and its associated implantational bleeding led to inadvertent biopsy.

Of the thirty-six patients whose responses to therapy were judged only by the occurrence of pregnancy, six became pregnant. Four of these pregnancies occurred during the first series of therapy. Two occurred during the second series of therapy. Accordingly, the fifty patients yielded a total of nine pregnancies, or 18 per cent of the patients treated became pregnant. A total of thirteen series of therapy, or an average of 1.44 series per patient, was given the nine patients.

Four of the nine pregnancies resulted in term deliveries of healthy children; one resulted in a stillbirth at five months, the cause being a true knot in the cord; and four resulted in abortions at about the third month.

Discussion

Those patients with anovulatory ovarian failure, characterized by diverse types of estrogenic bleeding, supply our most clear-cut data of the effectiveness of one-two cyclic gonadotropic therapy. They are included in the second and third groups and in the first subgroup of the fourth group, i.e., those with infrequent and/or scanty bleeding, those with prolonged and/or excessive bleeding and those with ovarian sterility characterized by estrogenic bleeding.

The results which are reported in this communication warrant comparison with those of our report of September, 1941:

Patients With Infrequent and/or Scanty Bleeding.—Present report: Positive responses in four of thirteen patients, or 30.8 per cent. *September, 1941, report:* Positive responses in five of eight patients, or 62.8 per cent.

Patients With Prolonged and/or Excessive Bleeding.—Present report: Positive responses in fifteen of thirty-one patients, or 48.5 per cent. *September, 1941, report:* Positive responses in seven of eighteen patients, or 38.9 per cent.

Patients With Ovarian Sterility Characterized by Estrogenic Bleeding.—Present report: Positive responses in seven of fourteen patients (including four pregnancies), or 50 per cent. *September, 1941, report:* Positive responses in three of three patients (including two pregnancies), or 100 per cent.

Total Patients of the Three Groups.—Present report: Positive responses in twenty-six of fifty-eight patients, or 44.8 per cent. *September, 1941, report:* Positive responses in fifteen of twenty-nine patients, or 51.7 per cent.

These data indicate, therefore, that an expansion of the number of patients treated with one-two cyclic gonadotropic therapy has not altered markedly our total percentage salvage from that reported in September, 1941. In our analysis of the total data which comprise this report we have been more critical, perhaps, than in that of the previous report. This may account in part for some differences in final figures.

The present report differs from the previous one by presenting data upon a group of fifty women with ovarian sterility which is presumed to be related to bleeding from immature progestational endometriums. The fact that nine of these fifty women became pregnant during one-two cyclic gonadotropic therapy appears to justify our diagnostic assumption, certainly in these nine women. The records of the other forty-one patients of this group who did not become pregnant under one-two cyclic gonadotropic therapy are interesting. Only five of these ultimately became pregnant. Four of the pregnancies occurred three months after the last series of one-two cyclic gonadotropic therapy and one, six months after the last series of treatment. It is considered unlikely, therefore, that the treatment which these patients received resulted in the pregnancies. We cannot, and have not, related these pregnancies to therapy. It is obvious that our diagnostic ability in this group is not good since only 18 per cent of the patients we treated upon our theory of endocrine sterility actually became pregnant. We believe, however, that to salvage pregnancies in 18 per cent of a group of patients, which previously had been accepted by us as having essentially normal ovarian function, represents a distinct addition to the total salvage of pregnancies from couples of low fertility.

When we consider those patients with ovarian sterility in association with estrogenic bleeding, we find that, of the seven patients who did not yield positive responses to one-two cyclic gonadotropic therapy, none became pregnant. Five of the seven patients who did respond positively to therapy became pregnant. Four of these pregnancies were relatable directly to treatment. Therefore, the seven patients who responded positively yielded the only pregnancies in this group, that is, a total of five pregnancies.

When the two groups of patients with ovarian sterility are combined, that is, those who bled from immature progestational endometriums and those who bled from estrogenic endometriums, we find that a total of thirteen pregnancies in sixty-four patients was attributable to one-two cyclic gonadotropic therapy, an incidence of pregnancies of 20.3 per cent in the patients with ovarian sterility.

Results of treatment of the group of patients with deficient sexual maturation associated with nonoccurrence of menarche were quite poor and were in line with pretreatment expectations. It was thought that these patients probably represented a group in which intrinsic ovarian inadequacy rendered stimulatory therapy quite unlikely to be successful. All forms of endocrine therapy apparently fail to effect full salvage in this group.

A statement about the allergic propensities of preparations of equine gonadotropin is in order. The practice of doing skin tests before administration of each series of this therapy is justified; however, only one patient to whom we have attempted to give equine gonadotropin proved so allergic that it was impossible to carry on treatment. This patient, obviously, is not included in this series. She had a long history of asthma and allergy. The patient gave a very positive skin test and, because of this and her history, no attempt was made to treat her.

All of the severe reactions which have been described by other workers have followed the intravenous administration of equine gonadotropin.¹² All of our treatments with this gonadotropin have been given intramuscularly.

Finally, some statement is indicated regarding the mechanism of action of one-two cyclic gonadotropic therapy. This may be an expression of a synergism between equine and chorionic gonadotropins. When full follicular maturation has been secured from ten days of equine gonadotropin therapy, ovulation and normal corpus luteum development and function follow the administration of chorionic gonadotropin. Our experience with pregnancies, which have occurred during this therapy, leads us to believe that ovulation occurs within twenty-four to forty-eight hours after the initiation of chorionic gonadotropin fraction of the treatment schedule. The one-two gonadotropic system of therapy may be viewed as duplicating the normal biphasic cycle of pituitary gonadotropic activity.

The dosage schedules which we have employed were selected rather arbitrarily. There is no reason, however, to believe the dosages are too large, since in no patient have we encountered undue ovarian enlargement or cystic change. Larger doses are being investigated and the results of their use will be reported later. They may enhance our salvage rates.

Summary and Conclusions

A total of 116 hypoovarian patients, whose ages placed them in the adolescent or reproductive epochs, was treated by the sequential and cyclic administration of equine and chorionic gonadotropins. The following results were obtained:

1. Only one of seven patients with deficient sexual maturation and non-occurrence of menarche (hypoestrogenism) yielded a progestational endometrium during therapy.

2. Four of thirteen patients, or 30.8 per cent, with infrequent and/or scanty estrogenic uterine bleeding yielded progestational endometria during therapy.

3. Fifteen of thirty-one patients, or 48.5 per cent, with prolonged and/or excessive estrogenic bleeding yielded progestational endometria during therapy.

4. Seven of fourteen patients, or 50 per cent, with cyclic estrogenic bleeding and ovarian sterility yielded positive responses, including four pregnancies, during therapy.

5. Nine of fifty patients, or 18 per cent, with cyclic bleeding from immature progestational endometria became pregnant during therapy.

The following conclusions appear warranted:

1. Patients with hypoestrogenism (as illustrated by those with deficient sexual maturation) respond poorly to this system of gonadotropic therapy.

2. Patients with anovulatory ovarian failure without hypoestrogenism (as illustrated by those with diverse types of estrogenic bleeding) respond well to this system of therapy: a total of 44.8 per cent yielded progestational endometria.

3. A small percentage (18 per cent) of sterile women, whose bleeding from immature progestational endometria constitutes the only significant finding upon their surveys or those of their husbands, become pregnant when treated with one-two cyclic gonadotropic therapy.

References

1. Hamblen, E. C.: AM. J. OBST. & GYNEC. 40: 615, 1940.
2. Hamblen, E. C.: AM. J. OBST. & GYNEC. 41: 495, 1941.
3. Hamblen, E. C., Cuyler, W. K., Wilson, J. A., and Pullen, R. L.: J. Clin. Endocrinol. 1: 749, 1941.
4. Hamblen, E. C.: ref. by J. P. Pratt in Sex and Internal Secretions, ed. 1, Baltimore, 1932, Williams & Wilkins Co., pp. 900-901.
5. Hamblen, E. C.: Virginia M. Monthly 60: 286, 1933.
6. Hamblen, E. C., and Ross, R. A.: AM. J. OBST. & GYNEC. 31: 14, 1936.
7. Hamblen, E. C., and Ross, R. A.: Endocrinology 21: 722, 1937.
8. Hamblen, E. C.: Endocrinology 24: 848, 1939.
9. Davis, M. E., and Koff, A. K.: AM. J. OBST. & GYNEC. 36: 183, 1938.
10. Hamblen, E. C., Cuyler, W. K., Wilson, J. A., and Pullen, R. L.: J. Clin. Endocrinol. 1: 742, 1941.
11. Mack, H. C.: J. Clin. Endocrinol. 3: 169, 1943.
12. Bickers, W.: J. Clin. Endocrinol. 1: 852, 1941.

(A related paper will be included in the next issue.)

THE EFFECT OF RESPIRATORY STIMULANTS IN THE NEWBORN INFANT

KHA TI LIM, M.D., AND FRANKLIN F. SNYDER, M.D., CHICAGO, ILL.

*(From the Departments of Pharmacology, and Obstetrics and Gynecology,
University of Chicago)*

AMONG the methods commonly employed for the resuscitation of asphyxiated infants at the time of birth, the use of drugs which stimulate respiration has been extensively tried. Clinical trial has left considerable uncertainty, however, both as to their effectiveness in overcoming respiratory depression and as to the margin of safety from the danger of overdosage.

Various considerations have prompted the use in asphyxia neonatorum of drugs such as alpha-lobeline, coramine, caffeine, metrazol, and cyanide. The recognition in recent years of the importance of reflex control of respiration involving the carotid body mechanism has increased interest in the possibility of affecting peripheral chemoreceptors rather than centering attention merely upon the hydrogen ion concentration or the carbon dioxide tension of the blood. There is evidence that the carotid body receptors are more resistant than the cells of the center to depression by narcotics, anoxia, and excessive CO₂ (Comroe and Schmidt, 1938¹). Consequently, extensive trial of pharmacologic agents which influence the nervous mechanism of respiration has been made (Marshall and Rosenfeld, 1937²). One of the major problems to be attacked from this new approach has been asphyxia in the newborn infant. Additional impetus was afforded by the reports of favorable response to analeptic agents when employed to combat overdosage of barbiturates in the adult (Werner and Tatum, 1939³). Great importance has been attached at times to the prompt initiation of the first gasp after birth and the efficiency of agents such as alpha-lobeline in accomplishing this result (Wilson, Torrey, and Johnson, 1938;⁴ Russ and Strong, 1941⁵). Metrazol, coramine, and alpha-lobeline have been used even before birth when signs of intrauterine asphyxia of the fetus appeared, the drugs being injected into the mother. By administration before birth it has been claimed that these drugs may aid in the prevention of asphyxia by effects upon the fetal circulation (Stuppy, 1940;⁶ Dörr, 1938;⁷ Nevinsky, 1937¹²).

Under clinical conditions the role of stimulant drugs in the resuscitation of newborn infants has been difficult to evaluate because of the numerous complications which are associated with delivery, such as anesthesia, anoxemia, and mechanical trauma. In the case of failure of resuscitation, the question arises as to whether or not adequate dosage was administered, or, on the other hand, whether the margin of safety was exceeded and the toxic effect of these powerful drugs was exerted. In the event of survival it has been difficult to demonstrate that these drugs effectively influenced the outcome.

The present investigation is an attempt to determine the effect upon the *normal* newborn infant of various respiratory stimulants, including alpha-lobeline, coramine, metrazol, caffeine, and cyanide. The aim in the present experiments is first, to take into account the peculiarities of the newly born animal in response to these powerful agents; second, to eliminate numerous complicating factors commonly associated with clinical trial.

Method and Material

Newborn rabbits were used in the present experiments. In order to record kymograph tracings of the rate and depth of respiratory movements, the entire body of the animal below the neck was enclosed in a small plethysmograph connected with a recording tambour as previously described (Rosenfeld and Snyder, 1938⁸). The animal was placed on his back in horizontal position with arms and legs fastened to a rigid board. The external jugular vein was readily exposed for injection, and the drugs were administered intravenously by a syringe with graduations of 0.01 c.c. Control injections of Ringer's solution were made throughout. The rate of administration was rapid, the injection being completed within a minute.

After the immediate response to various drugs had been tested in the plethysmograph, the animals were removed and remained under observation in order to detect more remote effects or failure to survive.

The observations are based upon 83 newborn rabbits obtained from 41 litters. In one group consisting of 57 newborn obtained from 26 litters, pentobarbital sodium in dosage of 20 to 30 mg. per kilogram was injected subcutaneously one hour before the respiratory stimulants were tested. After this dosage the general activity of the newborn animals was reduced sufficiently to afford tracings of the respiratory movements which were much less obscured by struggling movements than in a control series in which pentobarbital was not given. Furthermore, since barbiturates are widely used during labor, it is of added interest to observe the responses of the newborn to respiratory stimulants under conditions resembling those of clinical trial. In a second group consisting of 26 newborn of 15 litters, premedication was omitted. All litters were from animals which were mated in the laboratory and hence the age of the offspring was accurately known. Observations were made within twenty-four hours following birth. In addition to the newborn animals, a series of rabbits was studied during the later neonatal period at a time when respiratory responses were well established. In this group there were 21 rabbits obtained from 13 litters ranging in age from about 1 to 4 weeks and varying in weight from 75 to 320 grams.

Observations

Alpha-lobeline.—In newly born rabbits the intravenous injection of alpha-lobeline* was followed by disturbances of respiration, but it was difficult to determine a dosage at which stimulation occurred as indicated by increase in rate and amplitude of respiratory movements. Furthermore, the changes in respiration were brief, usually lasting less than a minute unless the convulsive level of dosage was reached. Thus, in Fig. 1, the respiratory movements were recorded following injection of the same animal with different dosages. Administration of 0.05 mg. of alpha-lobeline failed to increase the rate and amplitude of respiration. However, merely twice this amount, or 0.10 mg., resulted in transient depression of respiratory movements and convulsive seizures. In testing responses at various levels of dosage a single injection of one animal was made in many experiments, rather than repeated injections, and

*Ingelheim, Germany.

TABLE I. RESPONSE OF NEWBORN RABBITS TO RESPIRATORY STIMULANTS

DRUGS	NEWBORN RABBITS (NO.)	LITTERS (NO.)	MINIMAL EFFECTIVE DOSE (MG./KG.)	MINIMAL CONVULSIVE DOSE (MG./KG.)	RATIO OF		SURVIVAL
					M. C. D.	M. E. D.	
α -Lobeline	12	4	2	4	2		?
Coramine	13	8	100	300	3		?
Caffeine	14	6	100	200	2		?
Metrazol	14	4	100	200	2		+
Cyanide	4	4	0.05	0.15	3		+

Premedication: Pentobarbital sodium 20-30 mg./kg. subcutaneously.

.05 LOBELIN

.10



5 SEC.

Fig. 1.—Effect of alpha-lobeline upon respiration of a newborn rabbit. Intravenous injection of 0.05 mg., i.e., 1 mg./kg. failed to increase rate or amplitude of respiration; 0.10 mg. in the same animal resulted in depression. Premedication: pentobarbital sodium 20 mg./kg. subcutaneously.

.01

LOBELIN

.10

.20



5 SEC.

Fig. 2.—Effect of alpha-lobeline upon respiration of three newborn rabbits at different dosage levels: (1) 0.01 mg., i.e., 0.20 mg./kg. intravenously; (2) 0.10 mg., i.e., 2.0 mg./kg. intravenously; (3) 0.20 mg., i.e., 4.0 mg./kg. intravenously. Failure of stimulation. Premedication: pentobarbital sodium 20 mg./kg. subcutaneously.

usually littermates were used. Despite the use of fresh animals, results as illustrated in Fig. 2 show failure to obtain stimulation of respiration after a dosage of 0.01 mg., after 0.10 mg., and finally after 0.20 mg. of alpha-lobeline at which level convulsions occurred. The series included 12 newborn rabbits obtained from 4 litters. (Table I.)

When premedication with pentobarbital sodium was omitted, convulsions were noted following a dose of 0.10 mg., i.e., 2 mg. per kilogram; and irregular respiratory movements but not definite stimulation followed a dose of half this amount. The group included 11 newborn obtained from 6 litters.

Coramine.—Following the injection of 5 mg. of coramine,^{*} respiratory movements showed transient changes lasting less than a minute. As the dosage was increased, the depth of breathing rather than the rate showed some increase (Fig. 3). Convulsions appeared at a dosage level which was about three times the minimal effective amount. The group included 13 newborn obtained from 8 litters.

When pentobarbital sodium was not given, convulsions were observed following a dose of 1 mg., i.e., 20 mg. per kilogram; no definite stimulation of respiration was noted at lower dosage levels. Observations were made on 6 newborn obtained from 4 litters.

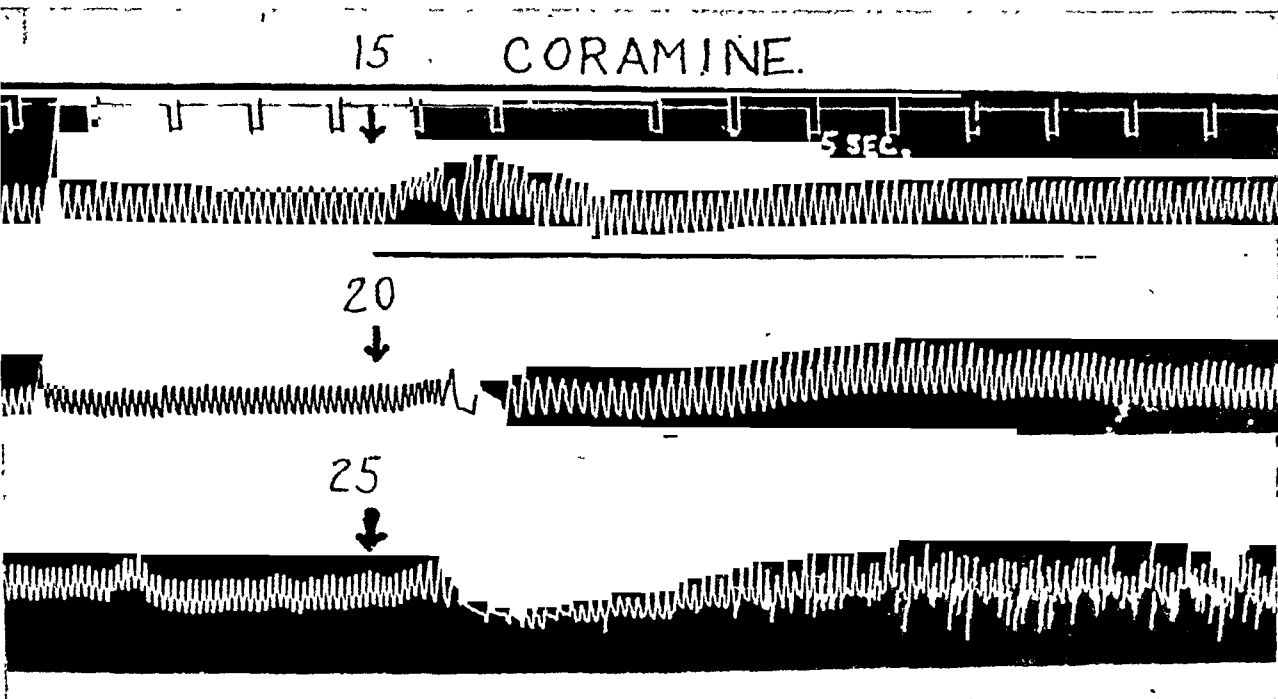


Fig. 3.—Effect of coramine upon respiration of the same newborn rabbit at various dosage levels: (1) 15 mg., i.e., 0.3 Gm./kg. intravenously; (2) 20 mg., i.e., 0.4 Gm./kg. intravenously; (3) 25 mg., i.e., 0.5 Gm./kg. intravenously. Premedication: pentobarbital sodium 20 mg./kg. subcutaneously.

Caffeine.—Following administration of 5 mg. of caffeine sodiobenzoate,[†] respiratory movements showed an increase in depth but not rate (Fig. 4). The changes disappeared within a period of less than a minute. As the dosage was increased, breathing became deeper but not more rapid. Convulsions were noted at a dosage level which was twice that of the minimal effective amount. Recurrence of deep gasps with definite periodicity was a characteristic effect of caffeine in the entire series. The group included 14 newborn obtained from 6 litters.

In the absence of pentobarbital sodium, convulsions were noted after a dose of 5 mg., i.e., 100 mg. per kilogram, and slight increase in depth of respiration was seen after one-half this dosage. Four newborn from 2 litters were studied.

Metrazol.—The injection of 5 mg., or 100 mg. per kilogram of body weight, of metrazol[‡] was followed by an increase in rate and amplitude of respiratory movements which persisted for a period of less than a minute. Administration of twice this amount, namely, 10 mg., resulted in striking convulsive seizures (Fig. 5).

When pentobarbital sodium was omitted, convulsions were noted with doses ranging from 0.5 to 2 mg., or 10 to 40 mg. per kilogram, in a group of 5 newborn from 3 litters.

*Ciba Pharmaceutical Products, Inc.

†Sharp & Dohme, Inc.

‡Billhuber-Knoll Corporation.

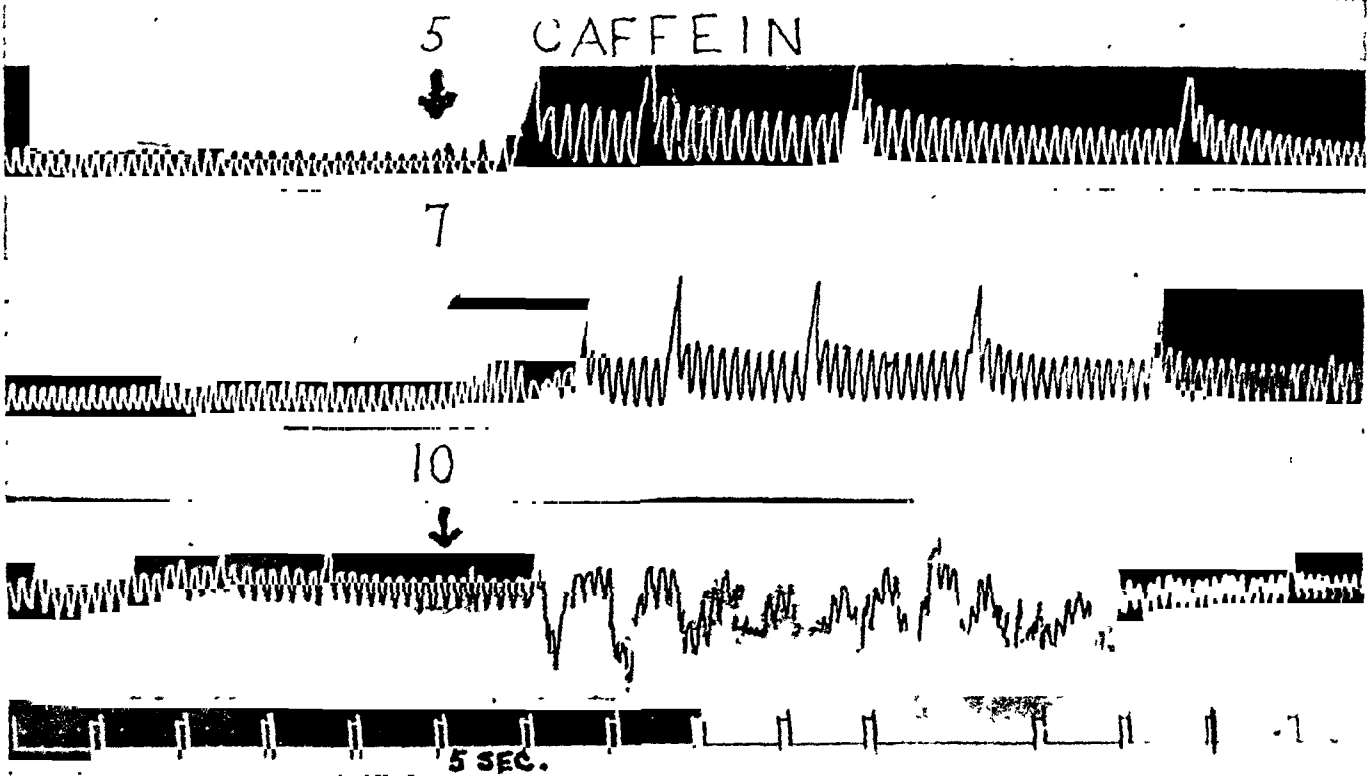


Fig. 4.—Effect of caffeine sodiobenzoate upon respiration of the same newborn rabbit at various dosage levels: (1) 5 mg., i.e., 0.1 Gm./kg. intravenously; (2) 7 mg., i.e., 0.14 Gm./kg. intravenously; (3) 10 mg., i.e., 0.2 Gm./kg. intravenously. Premedication: pentobarbital sodium 20 mg./kg. subcutaneously.

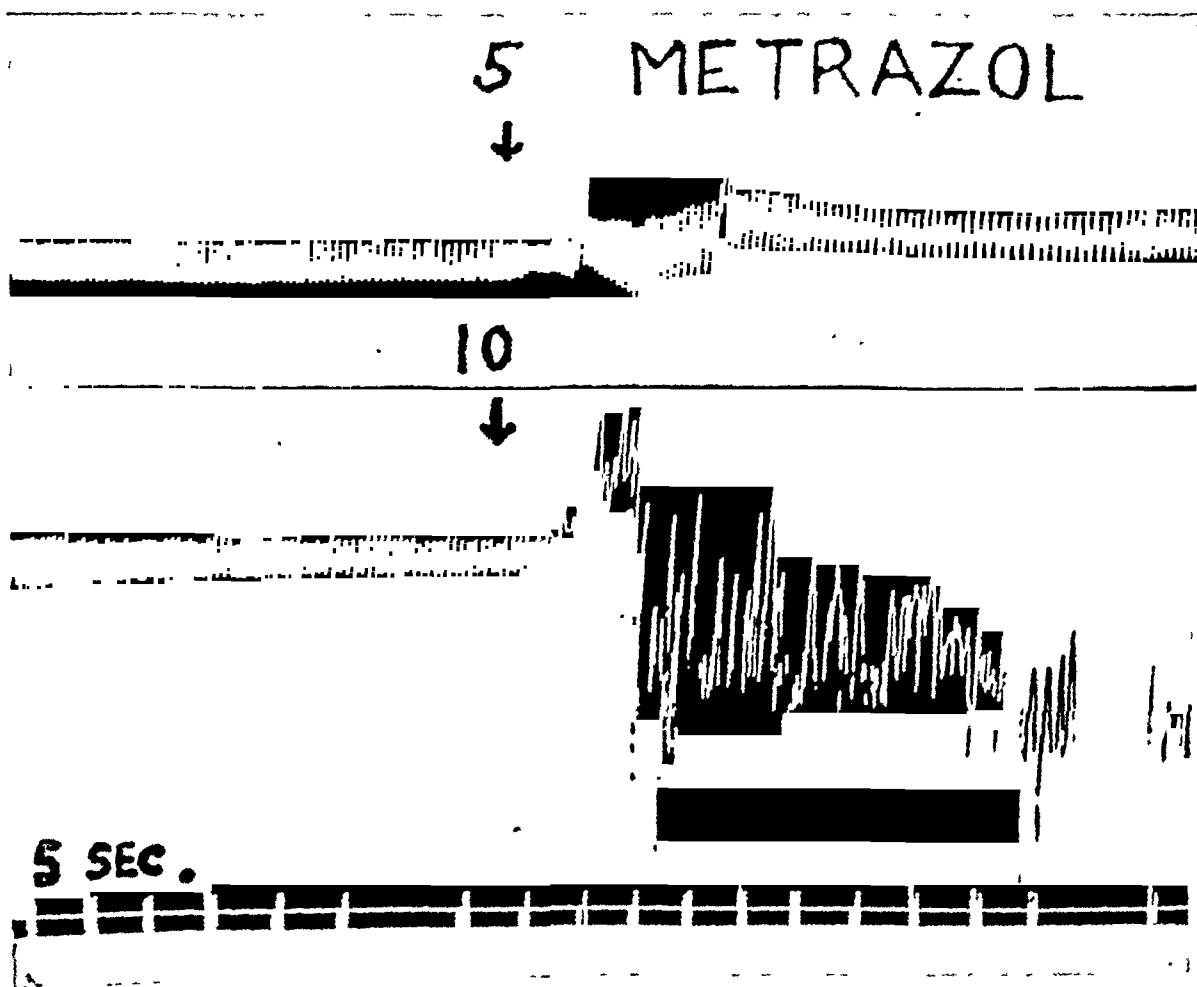


Fig. 5.—Effect of metrazol upon respiration of the same newborn rabbit. Intravenous injection of 5 mg., i.e., 0.1 Gm./kg. gave an increase in rate and amplitude, while twice this amount resulted in convulsive seizures. Premedication: pentobarbital sodium 20 mg./kg. subcutaneously.

Cyanide.—The response to injection of sodium cyanide and pyruvic acid cyanhydrin, with which Dr. Morris Rosenfeld of the Department of Pharmacology of the Johns Hopkins University provided us, was marked by definite stimulation of respiration, both depth and rate being increased. The effect was not prolonged, however, lasting about a minute or less. The margin was not large between the minimal stimulating dose and the depressant or convulsive level. Administration intravenously of 0.0025 mg. sodium cyanide, i.e., 0.05 mg. per kilogram, gave stimulation, while irregular convulsive movements followed a dosage three times as great, or 0.15 mg. per kilogram. Following 0.05 c.c. of 0.016 molar cyanhydrin, stimulation occurred, while twice this amount, or 0.10 c.c., resulted in convulsions (Fig. 6). Observations were made on 4 fetuses obtained from 4 litters.

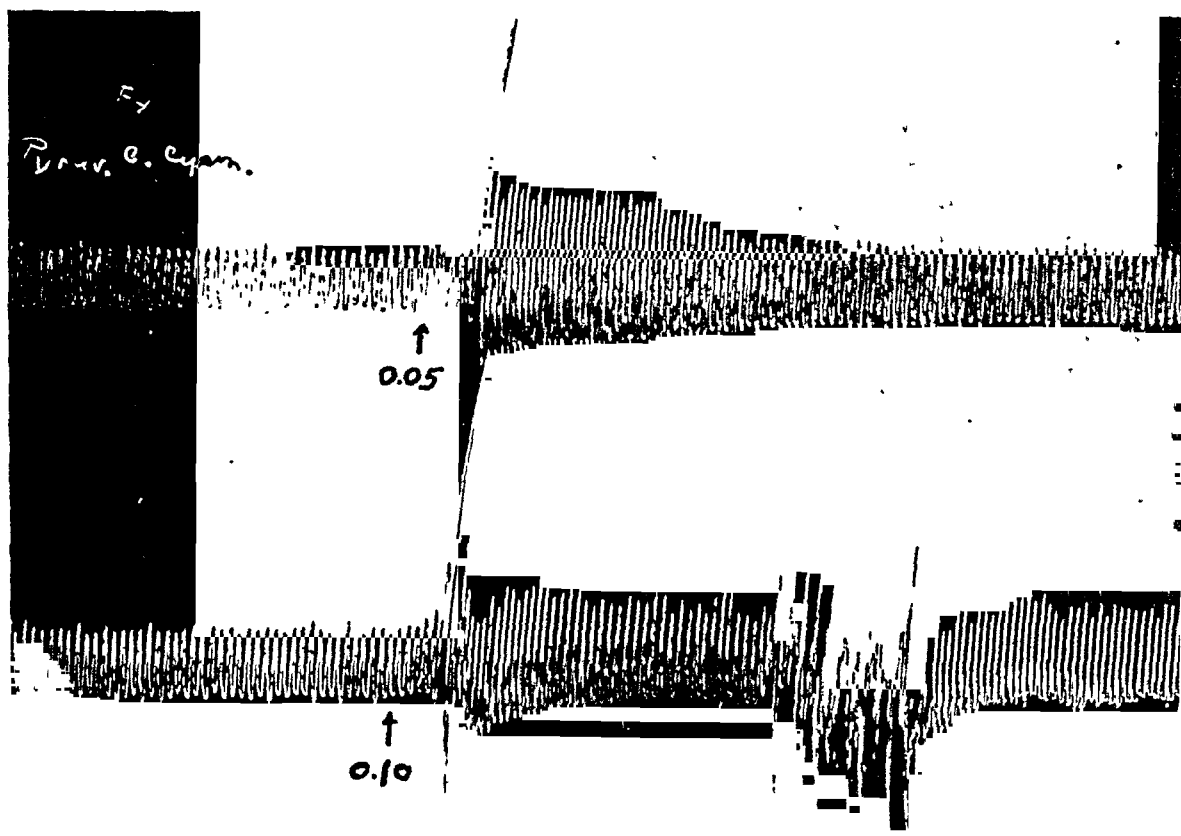


Fig. 6.—Effect of pyruvic acid cyanhydrin upon respiration of the same newborn rabbit. Intravenous injection of 0.05 c.c. of 0.016 molar solution gave definite increase in rate and amplitude, while twice this amount was followed by convulsions. Premedication: pentobarbital sodium 20 mg./kg. subcutaneously. Kymograph speed, 6 seconds = 1 centimeter.

Suckling Animals.—The respiratory responses were observed in a group of suckling animals in order to detect any marked alteration in reaction after survival for one to four weeks in the extrauterine environment. Pentobarbital sodium (20 to 30 mg. per kilogram) was injected subcutaneously an hour before the experiment. The results with the various drugs showed no striking change in sensitivity of the animals. The margin between the minimal effective dose and the convulsive dose remained about the same as was noted in the newborn. Observations were made with metrazol in 7 animals from 4 litters; with coramine in 6 animals from 4 litters; with caffeine in 2 animals of a litter; and with alpha-lobeline in 6 animals from 4 litters.

Late or delayed effects of the drugs were also investigated in addition to the immediate effect upon respiration as recorded by kymograph tracings. In view of the differences in rate of destruction or elimination of various drugs by the body, the animals were kept under observation for twelve hours or longer following injection. Failure to survive longer than a few hours following administration of the drug was noted frequently after alpha-lobeline, coramine, and caffeine. After metrazol and cyanide, however, the animals survived, despite the occurrence of convulsions.

Discussion

From the foregoing observations, three findings stand out clearly. First, it was difficult to demonstrate significant stimulation of respiration in the

sense of increase in rate and depth of breathing by the administration of alpha-lobeline, coramine, and caffeine; and following metrazol and cyanide, the slight stimulation was transient, lasting less than a minute. Second, a considerable hazard involved in the use of these drugs was found to be the narrow range between the dosage which affected respiration and that which caused convulsions. Two or three times the effective dose usually resulted in convulsions in animals which had received pentobarbital medication. In the absence of pentobarbital, the convulsive dose was smaller, being about one-half as great in the case of alpha-lobeline and caffeine, and about one-fifteenth as great in the case of coramine and metrazol. In the absence of premedication with barbiturate, a narrow range between an effective dose and a convulsive one was still demonstrable, although the threshold for the effects had shifted. Likewise, in the series of suckling animals, no marked change was noted in the range of safe dosage, which remained narrow even in the absence of premedication. Throughout the experiments, the minimal effective dose was determined in a given animal, and a fresh animal was used to determine the convulsive dose, thus eliminating any cumulative effect. Third, late toxic effects of certain of the drugs, alpha-lobeline, coramine, and caffeine, may result in the death of the animals after a period of hours following apparent recovery from convulsions. Survival occurred, however, after metrazol and cyanide despite the occurrence of convulsions.

In the presence of asphyxia the hazards involved in the use of respiratory stimulants are greatly increased. In the case of failure of resuscitation the question arises as to whether the dosage of the drug was adequate. It is well known that the threshold for an effective dose of these substances may be greatly raised by numerous anesthetic drugs which are administered during labor. Of significance in this connection is the finding in previous work that the fetus is peculiarly sensitive to anesthetic agents (Rosenfeld and Snyder, 1938⁹). When fetuses were observed directly through the wall of the unopened uterus, marked depression of the fetal respiratory responses occurred at a level of dosage at which maternal respiration showed little change. An additional factor to be considered in the etiology of fetal apnea at birth is anoxemia, which may be quite independent of narcosis (Snyder and Rosenfeld, 1937¹⁰). In the experiments on adult dogs in which extreme anoxia was induced rapidly by the breathing of 100 per cent helium instead of air, Eastman and Kreiselman¹¹ found that injection of alpha-lobeline, metrazol, or coramine failed to elicit a response until the anoxia was relieved by the administration of oxygen, whereupon convulsions appeared. In the emergency when resuscitation is required, repeated injections of the drugs may be prompted by weak or absent respiratory responses. High levels of dosage may be reached and the toxic action of these powerful agents may be elicited, although not recognizable immediately but only after delay of several hours. In brief, in asphyxia the respiratory responses of the newborn to these powerful agents may be masked; a level of dosage resulting in convulsions may be reached with little warning. The full extent of injury wrought by certain of these substances may be revealed only after a delay of several hours following injection.

In attempting to account for the considerable clinical trial which the respiratory stimulants have had in the treatment of asphyxia in the newborn infant, it is evident that evaluation of the success or failure of drug therapy has been difficult under conditions associated with birth. Uncertainty regarding the value of these drugs has not led to their total abandonment, however, but rather has resulted in the subordination of them to other methods of

resuscitation, especially various types of artificial respiration. What is significant is not so much that the slight or ineffective action of these drugs has been recognized, as that the toxicity of these powerful agents has often been overlooked.

The present experiments lend no support to the employment of alpha-lobeline, coramine, caffeine, metrazol, or cyanide in the resuscitation of the newborn infant. Outstanding factors influencing this conclusion are: (1) the relatively slight and transient nature of the increase in rate and depth of breathing elicited by these agents even under favorable circumstances; (2) the narrow range between an effective dose and one causing convulsions; (3) the shift of threshold for both the therapeutically effective and convulsive doses under the influence of narcosis and anoxemia, thereby confusing the calculation of dosage; (4) the insidious nature of the toxic action of certain of these drugs.

Conclusions

1. In newborn rabbits significant stimulation of respiration was difficult to demonstrate following alpha-lobeline, coramine, or caffeine; and following metrazol or cyanide the slight stimulation was transient, lasting less than a minute.

2. A considerable hazard involved in the use of these drugs was found to be the narrow range between the dosage which affected respiration and that which caused convulsions. Two or three times the effective dose usually resulted in convulsions in animals which had received pentobarbital premedication.

3. Injury resulting in death frequently followed convulsions which occurred after alpha-lobeline, coramine, and caffeine. Survival occurred after metrazol and cyanide despite the occurrence of convulsions.

4. The present experiments lend no support to the use of alpha-lobeline, coramine, caffeine, metrazol, or cyanide in the resuscitation of the newborn infant.

References

1. Comroe, J. H., and Schmidt, C. F.: *Am. J. Physiol.* 121: 75, 1938.
2. Marshall, E. K., and Rosenfeld, M.: *J. Pharmacol. & Exper. Therap.* 59: 222, 1937.
3. Werner, H. W., and Tatum, A. L.: *J. Pharmacol. & Exper. Therap.* 66: 260, 1939.
4. Wilson, R. A., Torrey, M. A., and Johnson, K. S.: *Surg., Gynec. & Obst.* 65: 601, 1937.
5. Russ, J. D., and Strong, R. A.: *Am. J. Dis. Child.* 61: 1, 1941.
6. Stuppy, C.: *Geburtsh. u. Frauenh.* 2: 528, 1940.
7. Dörr, H.: *Monatsschr. f. Geburtsh. u. Gynäk.* 107: 129, 1938.
8. Rosenfeld, M., and Snyder, F. F.: *Am. J. Physiol.* 121: 242, 1938.
9. Rosenfeld, M., and Snyder, F. F.: *AM. J. OBST. & GYNEC.* 38: 424, 1939.
10. Snyder, F. F., and Rosenfeld, M.: *Am. J. Physiol.* 119: 153, 1937.
11. Eastman, N. J., and Kreiselman, J.: *AM. J. OBST. & GYNEC.* 41: 260, 1941.
12. Nevinsky, H.: *Beilageheft zur Ztschr. f. Geburtsh. Gynäk.* 114: 1, 1937.

THERAPY IN HABITUAL ABORTION*

C. H. INGRAM, JR., M.D., F.A.C.S., PITTSBURGH, PA.

(From the Obstetrics Service of the Western Pennsylvania Hospital)

ONE of the most discouraging problems in the entire field of obstetrics has been that of habitual abortion. As is so often the case where results are unsatisfactory, writers upon this subject disagree concerning everything from definition through etiology and treatment, even to the very advisability of trying to do anything.

While Shute¹⁷ feels that one cannot surely recognize a habitual aborter until three or more successive pregnancies have terminated spontaneously at or before the sixteenth week, others are satisfied to make the diagnosis after two failures. As a matter of fact, one of my cases was treated after only one spontaneous abortion, but subsequent events, I feel, justify her inclusion in this report.

For obvious reasons, any exact figures on the incidence of spontaneous abortion, let alone habitual abortion, must be rather speculative. Malpas believes that 1 per cent of all pregnancies end in repeated abortions. Using this figure, the Council on Pharmacy and Chemistry of the American Medical Association⁵ surmises that in the United States alone there would be upward of 24,000 and possibly as many as 48,000 habitual abortions a year. Startling as these figures may seem from the standpoint of loss of life, they are as nothing when compared to the heartaches in the homes of those families where pregnancy after pregnancy is achieved, only to be followed almost inexorably by one spontaneous abortion after another. As a result, these patients are ready to cooperate in any reasonable regime that may be offered.

Several competent observers,¹¹ by histopathologic study of series of abortuses, have reported abnormalities in from 50 to 80 per cent of them. This fact being admitted, the problem of accounting for it arises. Mall feels that all of them are due to faulty implantation, while Meyer is of the opinion that the cause lies in an abnormality of the germ cells, either in the ova or the spermatozoa. Corner,¹¹ from a study of reproduction in swine, takes a middle-of-the-road course. He failed to find any histologic evidence of implantation abnormality, a strong argument for the poor germ cell theory, but he quite readily admits the possibility of chemical lesions proceeding from altered secretions without visible cytologic changes.

What then should be our attitude, in view of these two equally scholarly but widely divergent views? Malpas,¹ from a study of 115 abortion and stillbirth sequences, concluded that after two successive abortions 62 per cent would have a normal third pregnancy, after three 27 per cent would go to term, while after four only 6 per cent would go to a successful conclusion without any specific treatment. Quoting these figures, Rock¹² is rather skeptical of the value of any treatment. Many others, however, are more optimistic and report a very low incidence of fetal abnormalities among their successful cases. These reports make treatment seem of very decided value. Furthermore, they lend strength to Mall's theory of faulty implantation, while casting very real

*Read at the Pittsburgh Obstetrical and Gynecological Society meeting, Dec. 4, 1944.

doubt upon the defective germ cell theory of Meyer, at least in so far as it might be applied universally to habitual abortions.

Prior to 1918, all therapy was of an empirical nature and consisted primarily of rest in bed and sedation. In that year, J. C. Hirst of Philadelphia first began the use of an aqueous extract of corpus luteum. Since that time, others have attempted the use of one agent or another, with the hope of having a beneficial effect. Thus Rosenfeld¹³ and others felt that the blood serum of these patients lacked something necessary for the normal continuation of pregnancy. What this lack might be was a matter of pure conjecture but a number of patients were carried to term when they were given blood serum from normal healthy gravidas.

Thyroid gland has been used wherever there was a low basal metabolic rate. In addition, many writers have advocated its administration in doses of from $\frac{1}{4}$ to 1 grain a day as a routine measure in all cases, with the thought that it might help correct other endocrine dysfunctions, notably in the corpus luteum.

Shute has found an antiproteolytic substance in the blood serum of those who were about to abort or miscarry. This condition has been corrected, in some cases, by the administration of vitamin E either as 2 to 5 drams daily of cold pressed wheat germ oil or, more recently, 20 to 50 mg. of synthetic alpha tocopherol. He feels that this is of less value, however, in patients who are early aborters than in those who tend to lose their pregnancy at a later period. Collins¹ was unable to get consistent or conclusive results by using Shute's method on the blood serum. He, nevertheless, felt that one should make every possible effort to carry a habitual aborter to term, and so, while the test was abandoned, he continued to use 1 to $1\frac{1}{2}$ drams of wheat germ oil daily, with an increase to 8 to 12 drams if any evidence of threatened abortion appeared. This attitude is not far from accord with that of the Council on Pharmacy and Chemistry⁵ which summarized its report by saying that, while vitamin E therapy seemed promising, the results up to that time (1940) were not conclusive.

If, as Shute claims,¹⁶ the vitamin deficiency has a concomitant estrogen excess, that is, the antiproteolytic factor is estrogenic¹⁵; then progesterone, which might be called the physiologic antagonist of the latter,⁶ should be our long sought specific. Since becoming commercially available, as might be expected, both natural and synthetic progesterones have been widely used in this connection. Several observers have found that at the beginning of pregnancy the corpus luteum is very active but, during the third month it begins to atrophy and its function, at least in so far as the elaboration of progestin is concerned, is taken over by the placenta. This change occurs somewhere between seventy and ninety days after conception and thus coincides with the period during which the large majority of habitual abortions occur. Hamblen⁸ has found that the pregnandiol titers tend to fall either abruptly or gradually in most cases, prior to abortion. He has also been unable to elevate a low output or to prevent abortion by the administration of progesterone either alone or in combination with estrogens or chorionic gonadotropins. This writer consequently goes so far as to say that large doses of progesterone, by depressing the metabolism of intrinsic progestin, might precipitate abortion. Other writers such as Mason,¹¹ Campbell and Sevringhaus,³ and MacGregor and Stewart¹⁰ feel that progestin is of definite value.

If both vitamin E and progestin seem to be of value, the next logical step should be to combine them. Shute has done this with a number of his cases, as have others. Schmidt-Elmsdorff and Herold¹⁴ even go so far as to state that vitamin E, by its support of the endocrine system, seems to enhance the effect of the progestin, thus accounting for their use of both.

Clinical application in threatened abortion, whether habitual or not, has presented certain definite drawbacks, and early reports have been extremely disappointing. Wheat germ oil, according to Shute,¹⁵ must be fresh and given in adequate dosage to control the symptoms. While this is certainly a reasonable statement, to carry out its provisions is quite another matter. Hermetically sealed bottles of the oil may or may not be potent, while adequate dosage, as he has outlined it, becomes rather expensive if continued for a very long time. As for the three minim capsules so often used, adequate dosage almost resolves itself into a feat of deglutition. Shute has used a synthetic alpha tocopherol recently, but the patients to be mentioned later were given a mixture of alpha, beta, and gamma tocopherols distilled from vegetable oils and marketed as Tocopherex. Reasonably small doses of three to nine capsules or 9 to 27 drops a day sufficed. Since this series was begun, however, the manufacturer has withdrawn the liquid form from the market, so it is now available only in capsules, each containing 50 mg. of the mixture or the equivalent of 30 mg. of alpha tocopherol.

Another stumbling block in this combination therapy has been the unavoidable time lag between the onset of symptoms, whether cramps, bleeding, or both, and the administration of progestin to the patient. Irreparable damage may and probably does occur during this interval. This is particularly true in the event of bleeding, indicating, as it does, more or less separation of the chorionic attachment.

An experience with a threatened miscarriage pointed the way to a possible circumvention of this time lag in cases of habitual abortion. A primigravida in her sixth month was having frequent uterine contractions with the head well down in the pelvis and the cervix beginning to dilate. A hypodermic of morphine, $\frac{1}{4}$ grain, and an intramuscular injection of progestin in oil were given and she was left with a supply of 5 mg. tablets of anhydro-hydroxy-progesterone or pregnenolone. Her instructions were to take them three times a day and also at any time the cramps might recur. Although she had cramping for several days, each attack was promptly controlled by this oral medication, and after a week she was able to resume her regular normal activity. The pregnancy then proceeded uneventfully with the delivery of a normal girl just two days before her expected date.

The successful outcome of this case suggested the possibility of using this preparation in the prophylaxis of habitual abortion. As a result, the cases mentioned below were given 3 drops (or one capsule) of mixed tocopherols three times daily as soon as the first period was missed, 6 drops (two capsules) a dose for three days before the next period was due, 9 drops (three capsules) at a time during the days of the expected flow, tapering off with 6 drop doses for another three days, and then returning to the 3 drop level until time for the next period. This regime was continued at least until definite fetal movements were felt by the patient. The dose was also promptly increased to the 9 drop level in the event of either cramps or bleeding. Oral pregnenolone or pranone was also given in 5 mg. doses on the first three days of each expected period prior to quickening, plus an immediate dose should any evidence of threatened abortion occur. All patients were told to carry one or more tablets with them at all times and, in the event of either cramps or bleeding, to take a tablet, get off their feet, and call me. The emphasis was placed upon taking

the medication immediately. All were cautioned against undue exertion at any time and advised to take extra rest at the time of expected periods. All intercourse was prohibited. Thyroid was given to some but only as noted below.

Case Histories

CASE 1.—Mrs. M. L., aged 23 years, para O, gravida ii. First visit in this pregnancy Nov. 15, 1941 with her last menstrual period September 29. Six months prior to this she had had a spontaneous abortion on the eighty-first day, and had been advised to report as soon as a period was missed. There had been no special studies beyond physical and routine postpartum examinations. These were negative except for a very slight degree of endocervicitis. At this time she was put on the routine as outlined above. In spite of this she had slight cramps and spotting beginning on the eighty-second day and continuing for several days thereafter. Bed rest and the treatment already outlined resulted in a cessation of these symptoms, and she continued with an uneventful course and a normal boy delivered eighteen days prior to the expected date. This was the first case treated by this routine, and she has been included as an habitual aborter for three reasons. First she had one spontaneous abortion, second she had a threatened abortion while under treatment, and finally, when a third conception occurred a few months later, she did not bother to take any treatment and had a second spontaneous abortion.

CASE 2.—Mrs. H. W., aged 35 years, para i, gravida iv. First pregnancy normal, with a boy aged 13 years. During the depression she had used contraceptives. She first consulted me in her second pregnancy which was uneventful until the 110th day when she began to have cramps and a bloody discharge. In spite of bed rest, wheat germ oil, paregoric, and intramuscular injections of progestin at home, she continued to have these symptoms until they ended in an abortion on the 115th day. During her third gestation she began to take wheat germ oil at the start and was also given progestin at home from the onset of cramps on the 53rd day. In spite of this she miscarried on the 78th day. Following this second failure her basal metabolic rate was found to be -23 per cent. This was surprising as, clinically, she seemed to be exactly the opposite. On 1 grain of thyroid daily this was raised to -4 per cent, and the patient again attempted a pregnancy. This time she was given mixed tocopherols and pregnenolone in addition to her thyroid. She had both cramps and bleeding several times during the first five months but the pregnancy continued with delivery of a normal boy six days after the calculated date. She has had no further pregnancies.

CASE 3.—Mrs. G. W., aged 27 years, para O, gravida iv. First miscarriage was spontaneous at about the second month. A second one occurred at about six weeks. With her third pregnancy she began taking wheat germ oil at once and was given progestin at the second period time and again at home on the 77th day when she began to have a bloody discharge. This was to no avail as she aborted about fourteen hours later. Sterility studies seemed normal, and, because of many steps where she was living, she was advised to move. During her fourth pregnancy she took tocopherex from the start and pranone at period times and also as needed for cramps. This pregnancy resulted in a normal male infant five days beyond the expected date. No further pregnancies.

CASE 4.—Mrs. D. McK., aged 26 years, para O, gravida iii. She had miscarried at three and a half months, previous to moving to Pittsburgh. At her first visit in her second pregnancy, she was put on wheat germ oil and was given progestin at home on the 81st day for pains. She miscarried the following day. Sterility studies showed nothing abnormal except a -9 per cent basal metabolic rate. For this she was given $\frac{1}{4}$ grain of thyroid daily and also advised to move from the steep hill upon which she was living. With her third pregnancy she began taking mixed tocopherols as soon as her first period was missed, plus pregnenolone at period times and as needed for symptoms. She had a little bleeding at the time of her second period and some cramps at the third. After that she continued uneventfully to term, with delivery of a normal boy seventeen days after the calculated date. No further pregnancies.

CASE 5.—Mrs. A. C., aged 27 years, para O, gravida iv. Wheat germ oil and paregoric were advised for pink discharge on the 77th day of her first pregnancy, with abortion on the 81st day. She took wheat germ oil from the start of her second pregnancy but

aborted on the 73rd day. Thyroid, $\frac{1}{4}$ grain every other day, was begun for a -8 per cent basal metabolic rate. This was continued during her third pregnancy, together with wheat germ oil and pranone as needed. Nevertheless, she aborted on the 83rd day with the pathologist reporting a normal fetus. Four months later her basal metabolism was still -9 per cent, so her thyroid was doubled. All other studies were negative. With her fourth pregnancy she continued her thyroid through the fourth month. Tocopherex was taken for seven months and pranone at period times and as needed for cramps. She had several episodes of cramps and spotting during the first four months, but the pregnancy even survived the shock of having her brother reported missing in action (at the seventh month), and resulted in a normal living boy eleven days after the expected date.

CASE 6.—Mrs. M. A. L., aged 28 years, para i, gravida v. Her first pregnancy was uneventful, with a normal boy now 5 years of age. Her second ended in a spontaneous abortion at the third month. At about the fifth month of her third pregnancy there was so much abdominal tenderness that a laparotomy was done for a suspected ectopic gestation and she aborted a few days later. I first saw her with an incomplete abortion at about the third month of her fourth pregnancy. Following this, a general checkup failed to reveal any abnormality except a basal metabolic rate of -2 per cent. She was accordingly put on thyroid, $\frac{1}{4}$ grain daily, in addition to taking small daily doses of tocopherex before beginning her fifth pregnancy. In spite of this she had pain and tenderness in the left cornua together with spotting about six weeks after her last menstrual period. As a result she was hospitalized, and I too had a fear of a tubal pregnancy. While in the hospital she was given progestin in oil but after discharge she reverted to the oral pranone. Her tocopherol intake was, of course, stepped up to the upper level of dosage and on this regime her tenderness fully subsided. One further episode of watery discharge, probably urine, at the fourth month, kept us anxious for a few days, but from that time on everything proceeded smoothly. She continued her medication until within a month of term and delivered a normal girl five days after the calculated date.

Summary

Admittedly, the above is a short series of cases, yet the complete success in six pregnancies, where a total of sixteen previous pregnancies had yielded but two living babies, would seem very promising even if not necessarily conclusive. All patients but two (Cases 1 and 6) had had treatment in at least one prior unsuccessful pregnancy. Four of them were given desiccated thyroid in addition to the two preparations mentioned. One of these and one other were advised to move to avoid excessive climbs, but two others were successful in spite of steep hills and many stairs. Thus it might be postulated that thyroid is not indicated routinely but only in the presence of a lowered basal metabolic rate. Likewise environment is worthy of consideration, especially in a city having many hills and steep steps as does Pittsburgh.

These and any other indicated corrective measures should, of course, be employed. Yet it would seem that the principal basis for success rests with the combination of a potent preparation of vitamin E started in the very beginning or before, together with progestin or, rather, a progestin-like effect immediately available when needed.

The preparation of mixed tocopherols used in the above cases seems to have two very necessary properties. First, it seems to be reasonably stable, even in the liquid form. Second, its effect may be achieved without heroic-sized doses.

A progestin-like effect, in so far as the control of uterine contractions is concerned, can be obtained by the oral administration of pregnenolone. This avoids the necessity of trips to the physician's office at period time which is just when the patient should try to spare herself any unnecessary activity. It also has the added advantage of being constantly available should the patient begin to have any cramps or bleeding.

No ill effects were noted in the above series which might be ascribed to either of the preparations used. An interesting sidelight, however, is that five of the six successful pregnancies continued until after their expected dates.

Successful treatment of threatened abortion cannot be expected unless one does as Krohn and Harris,⁹ who provided each patient in their series with a supply of pregnenolone at the time of her first visit. Such a method would probably be of value in drastically reducing the incidence of spontaneous abortion, although I doubt its practicability as a routine measure. Anything short of this measure would probably be of little help, as, in my experience, these preparations are very seldom successful when begun after the onset of symptoms.

Conclusions

1. A combination of mixed tocopherols (Tocopherex) and oral pregnenolone (Pranone) has proved successful in a series of six cases of habitual abortion.

2. Treatment must be begun before the onset of any signs of threatened abortion, preferably as soon as the first period is missed or, better yet, as soon as a pregnancy is attempted.

3. This treatment is to be used in conjunction with, but not to replace, other indicated corrective measures. It is interesting to note, however, that no sedatives nor narcotics were found necessary.

4. No ill effects were observed, and all babies were normal.

5. This treatment is for the particular pregnancy, and probably will have no beneficial effects upon any future pregnancy.

References

1. Bachrach, A. L.: *Brit. M. J.* 1: 890, 1940.
2. Beavers, Herbert: *Texas State J. Med.* 36: 730, 1941.
3. Campbell, Ralph E., and Sevringhaus, Elmer L.: *AM. J. OBST. & GYNEC.* 39: 573, 1940.
4. Collins, C. G., Weed, J. C., and Collins, J. H.: *Surg., Gynec. & Obst.* 70: 783, 1940.
5. Council on Pharmacy and Chemistry: *J. A. M. A.* 114: 2214, 1940.
6. Council on Pharmacy and Chemistry: *J. A. M. A.* 116: 1523, 1941.
7. Falls, F. H.: *Surg., Gynec. & Obst.* 75: 289, 1942.
8. Hamblen, E. C.: *AM. J. OBST. & GYNEC.* 41: 664, 1941.
9. Krohn, Leon, and Harris, Joseph M.: *AM. J. OBST. & GYNEC.* 41: 95, 1941.
10. MacGregor, T. N., and Stewart, C. P.: *J. Obst. & Gynaec. Brit. Emp.* 46: 857, 1939.
11. Mason, Lyman W.: *AM. J. OBST. & GYNEC.* 44: 630, 1942.
12. Rock, John: *New England J. Med.* 223: 1020, 1940.
13. Rosenfeld, Samuel S.: *New York State J. Med.* 38: 440, 1938.
14. Schmidt-Elmsdorff, H. R., and Herold, L.: *Therap. d. Gegenw.* 81: 11, 1940.
15. Shute, Evan: *AM. J. OBST. & GYNEC.* 35: 249, 1938.
16. Shute, Evan: *Surg., Gynec. & Obst.* 75: 515, 1942.
17. Shute, Evan: *J. Obst. & Gynaec. Brit. Emp.* 49: 534, 1942.

6004 PENN AVENUE.

CATHARINA GEERTRUIDA SCHRADERS AND HER DIARY*

A Note on the History of Obstetrics and Especially on the History of Placenta Previa

ANDREW A. MARCHETTI, M.D.

THE composition of a diary has not been an uncommon product of the pen in many of history's ages. Much information about English life under the last Stuart rulers and William III may be obtained from the diary of John Evelyn. A more breezy and intimate mixture of incidents occurring during the first nine years of the Restoration may be sought in the now famous diary of Samuel Pepys. Diaries are not only sources of considerable historical interest and importance but in addition may attain, as Evelyn's and Pepys' have, a worthy place in the field of literature. Spanning the closing years of the sixteen hundreds and the greater part of the first half of the seventeen hundreds, another diary was written, written by a midwife. It is far from a literary achievement, but it is unique insofar as it portrays life in a community in the north of Holland and records the experiences of a woman dedicating about fifty years of her life to midwifery. It discloses facts that are a contribution to the history of obstetrics and especially to the history of placenta previa. Catharina Geertruida Schraders becomes more unique because until now she has escaped our notice and, except for two relatively short articles written about her, and the diary by two of her own countrymen, Dr. Arie Geyl of Dordrecht and Dr. Nuyens of Amsterdam, she has rested in oblivion.

Interest in the bibliography of the history of placenta previa led me to Geyl's paper, which was entitled "Catarina Gertruyt Schraders. Investigator of the Anatomical Character of Placenta Previa." This article, written in French, appeared in *Janus* in 1897 and informs us that Madam Schraders was among the first to investigate and appreciate the anatomic nature and clinical significance of placenta previa. Dr. Nuyens' article was published in 1926 in the *Nederlandsch Tijdschrift voor Geneeskunde* (the Netherlands Journal of Medicine). His paper, written in Dutch and entitled: "The Diary of Madam Schraders. A Contribution to the History of Midwifery in the Seventeenth and Eighteenth Centuries," is longer than Geyl's, has much more to say about the diary, and is more biographical and informative. It should be pointed out that these two references are the only available sources of information that concern the subject of this paper. Consequently, the substance of the story as it is told here is drawn almost entirely from the translation of these two articles, especially that of Nuyens. To Dr. Adriaan Barnouw, Professor of Dutch at Columbia University, the author wishes to express his thanks and gratitude for the invaluable assistance rendered in the translation of Madam Schraders' original passages and excerpts as they appeared in Nuyens' article. Originally, the hope was cherished that a photostatic copy of the entire diary might be procured from the Library of the University of Amsterdam in order that it might be translated and edited in the English language. However, when the request was made in February of 1940, the following reply dated March 9 was received from the librarian: "... we regret to inform you that in consequence of the international circumstances all our valuables are safely packed up,

*Read at a meeting of the New York Obstetrical Society, Dec. 12, 1944.

so that it is impossible to make photostatic copies of the Diary of Catharina Geertruida Schraders for you." Holland was invaded exactly sixty-two days later, on May 10.

First, let us consider a description and the disposition of the diary. According to Nuyens, one cannot attribute any beauty or elegance to its external appearance. The binding, obviously never meant to be a permanent one, simply consists of cardboard, and not of the period in which the diary was written. It is clear that it could be replaced when necessary. The diary is 544 pages long and is written entirely on fine solid old Dutch paper which has withstood a period of over two and one-half centuries without damage or deterioration except for an occasional wormhole. Here and there the ink is somewhat faded, but is still sufficiently clear for reading. Throughout, the script is by the same hand, even though at the age of 90 it is not so evenly written as fifty years earlier. Occasionally a page is found to be torn, but fortunately the text is left undamaged. The diary begins without an introduction or inscription and ends as abruptly on page 544 without a postscript.

This remarkable manuscript was bequeathed to the library of the Netherland Association for the Advancement of Medicine by Dr. J. J. Kiestra, physician from Ee near Dockum in Friesland. The collection of books and manuscripts belonging to this Association was stored in the Library of the University of Amsterdam. Dr. Kiestra had purchased the diary from the previous owner, Sybrand Fockema, physician of Leeuwarden, who had inherited it from Daam Fockema. The diary came into Daam Fockema's possession as a result of her marriage to Wytske Higt (b. 1710, d. 1780), a descendant of Thomas Higt who married Catharina Geertruida Schraders in 1713 and thereby became her second husband.

Catharina Geertruida Schraders was born in 1655. The name of her birthplace is not mentioned. She lived in Hallum in Friesland and married Ernst Willem Cramers. According to one of her notations, he was a surgeon. Cramers died on Feb. 4, 1692, whereupon in 1693 she began to practice midwifery. Why and under what circumstances she made such a decision is better related in her own words:

"In my 38th year, I was living at Hallum in Friesland where I had seen my good and learned husband, who was esteemed and loved by God and men, depart to his God to the great sorrow of myself and the inhabitants, leaving behind six little children when I was 36 years old. But then it pleased the Lord to select me for this important work, almost through the coercion of the good doctors and citizens, against which I had first offered resistance because it was such a grave matter and because I also thought that it was somewhat of a disgrace for myself and my relations, but in the end I have let myself be persuaded, besides it was pleasing to the Lord."

From the diary it is learned that she did her first delivery on Jan. 9, 1693. It was not an easy one to begin with, since she encountered a face presentation and a retained placenta, but in the end all went well. The doctors and citizens of her community, whose advice she had followed, were well aware of her ability. However, it remains unknown where and how she acquired the knowledge to practice. In former days the wife of a surgeon not infrequently was or became a midwife. It is very possible that she was instructed by her husband who was not only a surgeon but also, from her own words, "learned." Furthermore, the environs of Hallum were not devoid of some good scientific influence and progress, for van Deventer lived in Wieuwerd until 1690, while the skillful Cyprianus was professor at Franeker.

As soon as she had become established and settled as an accoucheur, she made a brief annotation of every delivery and would mention the name of the father and mother, the sex of the child, and the remuneration received for her services in each case. Whenever she was confronted with an unusual or difficult problem, she would make ample notes of it. At the end of each year, she added up her earnings, sometimes noted the expenditures, and then began the new year with a devout prayer. She was a minister's daughter and very religious.

On page 439 of the diary, one has evidence of some of the difficulties and hardships that she experienced in her obstetric practice in the rural districts. In 1693 she was called to help a widow at Wyns:

"On a Tuesday in 1693, I was called for the first time to Wyns to aid a widow whose husband had been Nicholas Jansen. A terrible storm was raging with a severe sleet. The three of us drove in a sleigh across the ice and could not keep on one's feet on account of the wind. Frozen branches hurt my legs so that the blood ran in my stockings. We finally reached Wyns after three hours' driving. We were almost dead and they carried me in and gave me brandywine. There was a good fire in the house which thawed me out a little. I asked for a box of snow with which I rubbed my hands and feet so long that at last life came back, otherwise I should have been crippled for the rest of my life. Having recovered I could also help the woman. The patient's late husband's brother had taken everything away from her and had told her that she should not bear the child. Hence, much depended upon the child's life, as it always does. The woman had a very difficult delivery as in a previous delivery at which she had the help of two midwives from Leeuwarden. I prayed to the Lord, and He heard me, and delivered the woman to the great joy of herself and me of a fine big daughter. This introduction to obstetrics was a painful one, but the Lord be praised, all was well and the woman recovered all her property."

The diary also reveals that she soon developed a widespread practice. On Oct. 6, 1694, she was summoned to Ameland for the delivery of twins and she wrote: "I had to go across the sea. When I entered the house, she raised up and said to me 'good woman, you came too late' and with that she died suddenly which frightened me. Oh, poor martyrs who come under such tortures of midwives!" That last exclamation betrays the fact that Schraders, too, was aware of the miserable and inadequate training of midwives, as well as how disreputable some of them were.

In 1693 she moved to Dockum. Ever faithful to her custom of indicating the occupation or profession of the husband of her patients, one learns that her practice included all ranks of society. Next to the name of a laborer or skipper, merchant or minister, physician or surgeon one finds representative names of some of the old noble families of Holland—the Harinxma's, van Ayluwa's, van Heert Tot Eversberg, Burmania's.

The first year of her practice in Dockum was the most profitable. On Jan. 1, 1699, she stated that during the successful year of 1698 she delivered 123 women from whom she received 310 guilders and 10 stivers. For surgery she received 103 guilders and 16 stivers, for cupping 22 guilders. She noted that there were twenty-three women from whom she got no pay. Other revenue which amounted to 16 guilders and 6 stivers brought the total income for that year to 452 guilders and 12 stivers. As Nuyens remarks, the bookkeeping was very primitive, but the addition sound. The remuneration for her services was niggardly. For instance, her maternity work was paid with single guilders and stivers, and the journey to Ameland only brought her five guilders. Only the nobility paid well, but then she frequently would remain a few weeks with a lying-in woman and consequently she would lose several other deliveries.

During January, February, and March of 1698 she delivered forty women, almost three a week. Considering the circumstances, such a striking capacity and energy for work merits one's admiration. It is further disclosed in the diary that she received patients in her home, for on May 2, 1701, she noted that Elizabeth Dhrooge, the wife of a coppersmith, Arnoldus Dhrooge, came to her house and was delivered there of a daughter for which she received 2 guilders and 10 stivers. On April 20 of the same year, she wrote that a lady from Gullickstaedt came to her saying that she was the wife of the secretary of the King of Denmark—"I delivered her of a boy. I was godmother to the child and he was named Jacob. Nine guilders and 16 stivers." It is interesting that the fee for the delivery of the wife of the King of Denmark's secretary was almost four times that of the coppersmith's wife.

In this brief but precise style, the diary goes on year after year. She took note of every special incident associated with a delivery and at the end of the year mentioned the results. At the beginning of 1703, she stated that at the age of 47 and after completing ten years of practice, she had delivered 840 children. On page 243 of the diary one reads that after eighteen years of practice, when she was 57 years old, she had delivered 1,937 babies for which she was paid 4,300 guilders.

Suddenly, in 1713, the continuity of the diary was interrupted. One notes, however, that a single delivery was done on January 13. She married Thomas Higt, aged 63, on February 13. By profession he was a gold- and silversmith and a member of the Assembly of Dockum. Madam Schraders was then 58 years old. In 1714 she remarked: "In my married state I aided a few in dire need." Her second husband died in 1721 and immediately after she resumed her practice. Except for this short interim while she was married to Thomas Higt, she kept up her work and diary for about a half century, up to 1745.

The first new annotation after she resumed practice was remarkable. On Sept. 26, 1721, a Mrs. Pousma, the wife of a cavalry captain, was delivered of a daughter and much to her amazement, six weeks later was delivered of a dead son. In the beginning of her second widowhood she was not too busy. This may be explained by the fact that many pregnant women had secured help from others. In 1723, for example, she had only twenty-three deliveries and in 1724 thirty-five. The year of 1727 was opened with a lamentation. She had reached the age of 72 and things were not going too well with her. More because of her old age, she invoked the help of God to supply the means for her relief and subsistence. Fortunately, she did have a better income that year. She assisted 73 women and earned 225 guilders. Beneath this income is found her expenditures which amounted to 220 guilders. It is noteworthy that nothing could stop her from carrying on her work, for it is also observed that during that same year she was very ill.

A most interesting notation is found on page 330. It has nothing to do with her work, but gives us an insight into the cost of living at that time. It is a small bill from Mrs. van Ayluwa for meat which was delivered to Madam Schraders. "In March she sent a calf's head, 6 stivers; in June she sent 17½ pounds of mutton at a half a stiver per pound." Living certainly was not expensive.

In 1733 she summarized her work and noted that at the age of 78 she had collected 8,500 guilders for "doctoring" and 1,100 guilders for surgery, "... and the Lord's blessings have been upon me." Even though one's living main-

tenance apparently was not costly in those days, nevertheless the sum of 10,000 guilders that she earned during forty years of hard work is small. Her practice diminished gradually. In 1738 she had only 14 deliveries; in 1740, 13 deliveries; in 1742, 18 deliveries. Her last notation appeared on Feb. 7, 1745, when she had attained the age of ninety. Her handwriting was still as legible and vigorous as it was fifty years earlier. Her obstetric career began with the delivery of a face presentation and ended with a transverse presentation.

Death was not so sudden as the beginning and the ending of her diary, for Catharina Geertruida Schraders did not die until Oct. 30, 1746, at the age of ninety-one.

Here is a woman then who for approximately half a century, and at times under the most trying circumstance, practiced midwifery in a community in Holland and among all ranks of society. A midwife who by the time she was 85 years old, as she stated on Sept. 18, 1740, had delivered 4,000 babies among them 64 sets of twins and three sets of triplets. Furthermore, she was one who always kept careful and exact notes of her work, revealing how seriously she persevered in her task. If she were known only for these deeds, that should be sufficient to acclaim our admiration. But she reaches the higher levels of our esteem, especially as an accoucheur, when one considers and analyzes the results of her work and the manner in which obstetrics was practiced in the seventeenth and eighteenth centuries. Up to this point, beginning with the description of the diary, what has been written is essentially a translation of Nuyens.

Let us cast a glance at the obstetrics of Madam Schraders' time. According to Miller, the two centuries between 1525 and 1725 in the history of obstetrics are thought of as the period of transition linking ancient or female midwifery to modern or male midwifery. Thus, it is a happy circumstance that Madam Schraders should fall in the last days of that revolutionary and evolutionary epoch of midwifery which ultimately flowered into the modern or scientific era of obstetrics. For centuries, after the best influences of Greek medicine had waned and were lost, and after Paul of Aegina who was the last of the few more noteworthy Greek authors on gynecology and obstetrics had died in 690, women alone governed the lying-in chamber, whereas men in the adjoining room looked at the horoscope and the stars. Pregnant women were committed to the ignorance, superstition, incantations, and barbaric practices of midwives during this gray antiquity. Later, true enough, men were called in for help in the most difficult cases, but obstetrics still was practiced by women. Thorndike points out and wishes to emphasize the fact that at the close of the sixteenth century superstitious ceremonial and magical rites and incantations had diminished greatly, so that the road to mathematical and scientific method was opened. Medicine and surgery began to make rapid strides in scientific progress, but obstetrics lagged behind. As a consequence, numerous pregnant women and many more babies continued to be the sacrifices of the ignorant and badly instructed midwife. In unfavorable outcomes these midwives were overburdened with reproach and abusive words, and not the least by surgeons. However, it is questionable whether these same surgeons who occasionally were invoked for assistance ever contributed anything constructive. They knew little more about obstetrics than the midwives whom they scorned.

The status of the midwife began to change with the appearance of Rösslin's *Rosengarten* in 1513. This was the first textbook on obstetrics that midwives had ever had to consult for their instruction. Walter Reiff's *Frauen Rosengarten* (1545) and Jacob Rueff's *Trostbüchle* (1554) were two of the better

known works that appeared after Rösslin's. Originally written in the vernacular, these treatises were translated into many languages and passed through numerous editions. However inadequate and unoriginal these early textbooks and their translations were, an influence was initiated in the proper direction inasmuch as they were written for the guidance and improvement of the midwife. Vesalius' *De Fabrica*, the works of Falloppio, Fabricius ab Aquapendente, Aranzio, and many other anatomists advanced the knowledge of female anatomy. As the knowledge and appreciation of female pelvic anatomy increased, surgeons began to turn more of their attention to obstetrics. In France, Ambroise Paré rediscovered version and extraction, Guillemeau further promulgated its use, and François Mauriceau entirely abandoned the practice of surgery to make a specialty of obstetrics. Scipio Mercurio in Italy became the first to state that a contracted pelvis was a definite indication for cesarean section. In Holland, van Deventer practiced orthopedics and obstetrics and now is acclaimed "the father of modern midwifery." William Harvey advanced the cause of obstetrics in England. Jules Clement with the indorsement and blessings of Louis XIV ultimately broke down the prejudices against the man midwife and established his place in the delivery room. Finally, the excellent textbooks of Mauriceau, Portal, de la Motte, and van Deventer raised obstetrics from its debased position and placed it, as Miller puts it, "on the road of true scientific reform based on exact knowledge and rational principles." In Holland the practice of obstetrics remained in the hands of midwives almost to the last years of the eighteenth century.

The criticism and condemnation directed toward midwives continues to be vehement. None could be more violent than Geyl's in a study on the instruction of midwives which he published in 1897. That there is justification in the greater part of this condemnation is unquestioned. Among the innumerable badly instructed and unscrupulous ones, however, there must have been a considerable number of good and able midwives deserving more than the contempt which was universally thrown at them just because they were midwives. Recall that even Madam Schraders first resisted the idea of becoming a midwife "because I also thought that it was somewhat of a disgrace for myself and my relations."

It was centuries before any one of them rose above the average capacity and ability of her sisters, but the close of the sixteenth century produced Louise Bourgeois; the last years of the seventeenth, Justine Siegemundin; late in the eighteenth century, Madame du Cordray; and in the beginning of the nineteenth century, Madame La Chapelle and Madame Boivin. Each one of these famous midwives, in addition, wrote a book on obstetrics meriting a place beside those of her male competitors.

It appeared necessary to insert this brief perspective of the historical background of the state and development of midwifery during Madam Schraders' time in order that she and an analysis of her work and results might be better projected and evaluated.

This pious, honest, modest, and conscientious woman says nothing about asepsis or antisepsis, nothing about narcosis in her diary. The use of forceps was little known if at all. In 4,000 cases, the placenta was found adherent 65 times. Credé's maneuver did not exist then, but she employed the procedure of inserting her right hand into the uterine cavity to separate and remove the placenta while the cord was held in the left hand, a method which was recommended by van Deventer, Portal, and others as a good one. She records 90 fetal

deaths, a fetal mortality of 2.25 per cent in 4,000 deliveries, which is creditable to say the least. Among the causes are mentioned: prolapsed cord 25 times, placenta previa several times, transverse presentations, obliquely contracted pelves, breech presentations, and monsters. There were 15 maternal deaths or a maternal mortality of 0.375 per cent (nearly four per thousand). On three occasions she was called and the mother was found moribund, on one occasion the mother was already dead. For the rest, puerperal infection is mentioned six times as the cause of the death of the mother, placenta previa (hemorrhage) twice, and tuberculosis of the lungs, convulsions (eclampsia?) and gangrene of the leg once each. Such an outcome is remarkable. It is impressive to note that the number of cases of infection is small. No word is mentioned of a special solution for the hands; but oil, butter, or green soap were ordered as a lubricant. It is possible, too, that the particular rural environment supplied a natural immunity to keep the fatal outcome of puerperal infection low. If her results are compared to those of the Maternité in Paris where the maternal mortality rate was between 10 per cent and 16 per cent during the eighteenth century, as Nuyens points out, even Geyl would admit that a pregnant woman was safer in the hands of the scorned and reviled midwife.

Only on eight occasions did she call upon the help of a surgeon.

She made a distinction between "the hook" and "the instrument."

It is clearly observed in her diary that she knew and followed van Deventer's *Novum Lumen* which was published in 1701.

She knew version and extraction, and it is extraordinary and of the greatest interest to obstetric history how she promptly understood the anatomic relationship and clinical implications of placenta previa as soon as she was confronted by this complication. She encountered her first case in August of 1701 and wrote:

"I was summoned to Hylles, to the wife of a merchant Rinck Eekes, after I had been called there several times because she had a hemorrhage; and when I was called the last time, I found her very weak and with intermittent large losses of blood, but finally she fell into labor; when I examined the case, I found the placenta ahead of the baby, but adherent, something which I had never heard mentioned nor which I had ever before experienced; I was obliged to peel it off; the baby was found lying across the cervix; I turned it and succeeded with a great deal of difficulty in extracting it by the feet; but the infant was already dead and the mother died a half hour later." Five years later she had the second case of placenta previa on August 1. She noted: "I found the placenta firmly adherent, in front of the baby; I prescribed immediate delivery, but asked for the assistance of a doctor. She was not in labor. The doctor stated that he wished to give her something to start labor. I said the baby was dead, he maintained that it was alive; I pushed aside the placenta after having detached it, found the feet and extracted the child to Dr. Eysma's shame who had insisted that the child was alive whereas it had already shown signs of maceration."

On Dec. 1, 1724, Gerrit Creemers de Ternaart consulted Madam Schraders about his wife who had been having continuous losses of blood for two weeks to the point where she would faint. Without hesitation she advised that the patient be delivered at once by the midwife in attendance. The midwife requested to know whether Madam Schraders had lost her mind in advising the delivery of a woman who had not yet begun labor. She lost no time in making any reply, but promptly went to the patient herself and when her colleague obstinately refused to follow her advice, then she took over and began the delivery. She found the placenta attached to the lower part of the uterus, detached it and

soon after the mother was delivered and saved. The baby was already dead. Geyl states that she reported six real cases of placenta previa and one doubtful one. At the time of her first case she waited until labor set in before attempting any exploration and action, but having in mind the fatal outcome of that case she acted more promptly thereafter. She was convinced that placenta previa should be treated at once regardless of labor or cervical dilatation and adopted the maxim: Act as soon as hemorrhage menaces to be fatal. It was not long ago that accouchement forcé was the form of therapy accepted and recommended by many distinguished and able obstetricians to combat placenta previa.

According to Fasbender, there can be no doubt that Paul Portal was the first to recognize the clinical significance and anatomic relationship of placenta previa. His *La Pratique des Accouchemens*, etc., was published in Paris in 1685. Haller translated it in Dutch in 1690. Portal's first observation on placenta previa occurred in 1672. Madam Schraders' first experience with placenta previa was dated August, 1701 twenty-nine years after Portal's first case, sixteen years after the appearance of his book, and eleven years after Haller's Dutch translation of it was published. Could Portal's *La Pratique* or Haller's translation of it have crossed her path? We believe not. Her own words state, as she described the findings in her first case, that it was something which she had never heard mentioned nor which she had ever before experienced. Geyl asserts that Madam Schraders recognized the condition independently of Portal, and that she and Portal not only pointed out the anatomy of placenta previa, but also recognized the clinical danger associated with it and understood the means to combat it.

With Nuyens this author is agreed when he writes that if Catharina Geertruida Schraders had been less modest and had lived in other surroundings, if she could have been better able to express herself in the language of the art of midwifery and had sought a publisher, then she might have given to posterity a book as good as most of her time. True, she did not write a handbook nor a treatise for midwives, but she did write a diary. Had her case reports ever been published, she might have acquired a name in the history of obstetrics worthy to be placed next to those of Bourgeois, Siegemundin, La Chapelle, Boivin, and others. She certainly was not less capable. Her diary gives us an insight into a remarkable human life and into the difficulties and hard existence of an ingenuous midwife who nevertheless by her wisdom practiced her calling. Her careful notations and her untiring work merit the recognition, gratitude, and admiration of posterity.

References

- Nuyens, B. W. Th.: *Het Dagboek van Vrouw Schraders*. *Nederl. Tijdschr. v. Geneesk.* 70: 1790, 1926.
 Geyl, A.: *Catharina Gertruyt Schraders*, *Janus* 1: 537, 1896.
 Miller, J. L.: *Renaissance Midwifery: The Evolution of Modern Obstetrics, 1500-1700*. *Lectures on the History of Medicine*, Mayo Foundation Lectures, Philadelphia, 1933, W. B. Saunders Co.
 Fasbender, H.: *Geschichte der Geburtschülfe*. Jena, 1906, Gustav Fischer.
 Garrison, F. H.: *An Introduction to the History of Medicine*, Philadelphia, 1924, W. B. Saunders Co.

PATHOGENESIS OF POSTABORTAL PERITONITIS

A Study of 61 Cases

HENRY C. FALK, M.D., F.A.C.S., AND GEORGE BLINICK, M.D., NEW YORK, N. Y.

(From the Gynecological Service of Harlem Hospital)

DURING the past fifteen years an intensive study of the clinical and pathologic aspects of the incomplete abortion has been conducted in this service. From this study two conclusions were reached. First, the uterine cavity is usually infected in incomplete abortions, whether spontaneous or induced, with or without fever. Second, all infected abortions may be divided into six groups depending on the pathology found and their clinical course.¹

These six groups are:

1. Abortion in which the infection is limited to the cavity of the uterus, which comprises 83 per cent of all abortions seen.

2. Abortion in which the infection spreads from the uterus but is still limited to the extraperitoneal structures. About 9 per cent of all abortions are of this group, which includes parametritis, pelvic cellulitis, extraperitoneal pelvic abscess, perivesical and perirectal exudates, etc.

3. Abortion in which the infection spreads from the uterus to the veins and where the predominant symptoms are the result of thrombophlebitis, with or without embolization. Parametritis is frequently an associated or causative lesion.

4. Abortion in which pathogenic bacteria have left the uterus and become secondarily implanted on the mural endocardium, heart valves, or pulmonary artery, and the infection is disseminated from this location. Visible evidence of either a pre-existing pregnancy or of infection in the uterus is often absent at autopsy.

5. Abortion in which the infection spreads from the uterus to the peritoneum, producing a general peritonitis.

6. Those cases in which the uterus has been perforated by an instrument. The pathologic findings depend upon the degree of infection, asepsis, trauma to adjacent organs, etc.

This present study is devoted to an analysis of the pathogenesis and the associated pathologic findings in the fifth group, i.e., general peritonitis. Many gynecologists include patients with parametritis and an associated peritoneal edema or local pelvic peritonitis in this group. The inclusion of such patients among those with generalized peritonitis is unsound from the viewpoints of the pathogenesis and morbid anatomy. Furthermore, a false impression is created in respect to the prognosis and the efficacy of treatment. The following discussion is therefore limited to those patients in whom generalized peritonitis followed abortion (exclusive of those secondary to perforation of the uterus.)

To formulate a concept of the problems of diagnosis and therapy of post-abortion peritonitis, it is important to determine how the infection spreads from the endometrium to the peritoneum. At necropsy only the end stages of the disease are evident; on the other hand, a clear analysis of the pathway of the infection during life may be impossible.

In postabortal disease the infectious process begins almost exclusively at the placental site and in the adjacent endometrium. This area is the seat of a suppurative process and may be converted in whole or in part into a shaggy, inflamed, or necrotic membrane to which portions of placenta, decidua, and blood are adherent. On microscopic examination there is marked necrobiosis of the

superficial layers with abundant leucocytes, chiefly polymorphonuclear in nature, and varying bacterial infiltration.

In postabortal peritonitis the peritoneal cavity usually contains a large amount of more or less turbid purulent fluid. The intestines are distended and reddened. In rapidly fatal cases, several liters of exudate may be found without evidence of localization of the infection. More often, pus pockets in various stages of organization occur in the lumbar gutters around the liver, in the cul-de-sac, and between the loops of small intestine. In late cases, very little free fluid may be present. A gelatinous exudate is spread throughout the peritoneum and causes the coils of intestine to adhere to each other. Localized pockets of pus may be found. The histologic findings are characteristic of purulent peritonitis and are without distinctive features.

How does the infection extend from the uterus to the peritoneum? In general, three modes of extension have been found: first, through the Fallopian tubes, second, through the parametrium, and third, through the myometrium.

1. *By Way of the Tubes*.—There has been considerable controversy as to whether or not fatal peritonitis can be conveyed from the uterus to the peritoneum by means of the tubes. Williams² stated, "In many autopsies I have seen upon women dead of puerperal infection, I have never seen one in which there was any evidence that infection occurred in this manner." Goodall³ postulated that puerperal infection which extends by continuity of epithelial surfaces is gonorrheal in origin. Halban and Koehler,⁴ in 69 cases of fatal puerperal peritonitis, found that spread of infection by way of the tubes alone occurred in twelve instances. Martland⁵ studied 53 cases of postabortal peritonitis and found that the tubes were involved in thirty-nine.

In an epidemic of puerperal sepsis with peritonitis, Watson⁶ states that the findings "point to a primary lymphatic infection." Extension via the Fallopian tubes is said by him to be more common in postabortal than in postpartum infection.⁷

In the present series, by far the most common pathway of extension (66 per cent) of infection from the cavity of the uterus to the peritoneal cavity was through the tubes. In these cases, the tubes are swollen, red, and tortuous. Occasionally they may even appear gangrenous. The fimbriated ends of the tubes are frequently patent. In rare instances, the fimbriae may be glued together with the formation of a small pyosalpinx. When cut in cross section, an exudate identical with that in the peritoneal cavity is present, and the folds of the endosalpinx are inflamed, edematous, and occasionally gangrenous or hemorrhagic. Histologically there is an intense, acute bacterial endosalpingitis. The villae are thickened, edematous, and infiltrated with polymorphonuclear cells. Often the epithelium is desquamated. Pseudogland formation is absent. The muscle coats are infiltrated with leucocytes. Apparently as a result of the generalized peritonitis, the serosal surface of the tubes as well as of the parametrium and the myometrium are all extremely inflamed and edematous.

CASE 1.—F. M., an 18-year-old nullipara, complained of abdominal pain, fever, and vomiting following an induced abortion two days prior to admission, Dec. 9, 1933. Menses had always been regular and normal. The last menstrual period had started seven weeks before. Examination disclosed signs of generalized peritonitis, and she died six days after admission. At autopsy the abdomen contained 3,000 c.c. of creamy yellow pus. The endocervix and endometrium were entirely gangrenous and foul-smelling. The tubes were enlarged to three times their normal size and contained a considerable amount of pus. The fimbriated ends of the tubes were open. The endosalpinx was hemorrhagic. The appendix was normal. The myometrium, parametrium, and ovaries were normal. There was no thrombosis of the pelvic veins.

2. *By Way of the Parametrium*.—Extension of the infection from a suppurative endometritis through the parametrium to the peritoneum was found much less frequently in this series.

Infection of the pelvic cellular tissue is essentially of lymphatic origin. There can be no doubt that "by comparison with the nongravid uterus the lymphatic channels of the gestational uterus, although probably not numerically increased, are obviously tremendously enlarged in calibre."⁸ Bacteria enter the lymph vessels from the infected endometrium

and produce lymphangitis and perilymphangitis. The surrounding connective tissue thereby becomes involved and an intense reaction occurs with leucocytic infiltration and much pouring out of serum so that the tissues become tense and edematous. (Parametritis or cellulitis of the broad ligaments.) A similar sequence may occasionally be observed as a result of infection originating in the open mouths of the venous sinuses of the endometrium. This causes thrombophlebitis and periphlebitis of the pelvic veins with extension to the cellular tissue of the parametrium. The gross and microscopic appearance of the lesion in cellulitis of the broad ligament associated with peritonitis is apparently identical with that of an uncomplicated parametritis, and has been described in detail elsewhere.⁹ The exudate may be limited to the broad ligaments, or may extend anteriorly to the prevesical space, posteriorly to the perirectal space, or upwards to the retroperitoneal space.

The histologic appearance is characteristic of cellulitis, that is, edema, fibrin formation, and perilymphangitic and perivascular infiltration. The exudate is often mononuclear in nature but may be frankly purulent. It is particularly abundant about the infected lymphatic vessels and occasionally in and about the veins. The tubes and myometrium may appear to be normal except for inflammation of the peritoneal surface.

CASE 2.—M. F., a 27-year-old primipara, was admitted Aug. 19, 1932, because of lower abdominal pain, vaginal bleeding, chills and fever for two weeks following abortion. Induction was denied. Examination of the abdomen revealed extreme distention, tenderness, and rigidity. On vaginal examination, resistance in the fornices and cul-de-sac was noted. Death ensued eight days after admission. At autopsy there was a considerable amount of greenish-yellow fluid pus with fresh fibrin in the abdomen. The intestines were matted together and greatly distended. The uterus was slightly enlarged. The uterine mucosa was necrotic and gangrenous and contained a placental site on the posterior fundal wall. The tubes appeared normal and contained a scanty mucoid secretion. Both broad ligaments showed a marked cellulitis with edema of the areolar tissue extending to the pelvic walls. The uterine sinuses were thrombosed but the pelvic veins were not involved. The other organs showed cloudy swelling.

CASE 3.—E. A., a 19-year-old primipara, was admitted March 17, 1932, with the chief complaint of abdominal pain, vaginal bleeding, and fever following an abortion induced with a catheter eight days previously. She appeared critically ill with generalized peritonitis and died three days after admission. A blood culture was negative. At autopsy, 500 c.c. of brown watery fluid was found in the peritoneal cavity. This contained free-floating thick fibrinous plaques; similar plaques were attached to the serosa of the viscera. The uterus was enlarged to the size of a six weeks' pregnancy and was soft and boggy. On opening the uterine cavity, gangrene of the endometrium was present. The tubes did not appear enlarged or inflamed. The pelvic lymphatics were beaded and enlarged. The retroperitoneal tissues were inflamed and edematous.

The vast majority of postabortal parametric infections remain extraperitoneal. Extension occurs via the lymphatics and along the endopelvic fascial planes. Hofbauer¹⁰ has shown that there is normally an increase in the number of wandering tissue cells (clasmato-cytes, macrophages) in the parametrium during pregnancy and interprets this as a means Nature may use to limit the spread of infection.

The mode by which infection leaves the parametrium to enter the peritoneal cavity is not clear. If the peritoneum is merely an extended lymph space, as Goodall states, and "the pelvic peritoneum communicates by a thousand ostia with the lymphatics of the subperitoneal spaces," then the mechanism is clear. There are, however, several objections to this theory. First, the presence of peritoneal stomata has not yet been indisputably proved.¹¹ Second, according to anatomic studies by Rouvière¹² the lymphatics of the cervix and corpus are connected with each other and with those of the tube and ovary, and empty into the aortic, external iliac, and hypogastric nodes. No mention is made of a peritoneal anastomosis. Third, carcinoma of the cervix and body of the uterus metastasizes primarily through the lymphatics and by direct extension to the parametrium.¹³ With further lymphatic extension the retroperitoneal nodes are affected, whereas the peritoneum is conspicuously free of metastatic involvement. The peritoneum may be implicated, not by lymphatic extension, but by direct invasion. It would seem, therefore, that a direct pathway of infection from the uterus through the lymphatics to the peritoneum has not been proved, although its possibility cannot be denied.

Halban and Koehler have stated that infection, whether of lymphatic or venous origin, may enter the general circulation and give rise to "metastatic" peritonitis. Watson and

Goodall have found that changes in the serous cavities, meningitis, pericarditis, pleurisy, and peritonitis, are more frequent with lymphatic than with venous spread. In the present series of cases, despite complete and careful autopsies, no evidence of infection has been seen in the serous cavities other than the peritoneum. There was not a single instance of pericarditis or pleurisy even though in several cases embolic lung abscesses were found associated with pelvic thrombophlebitis. Because of the absence of changes in the other serous cavities and the lack of evidence of diffuse embolization, transmission of the infection via the bloodstream does not seem adequately to explain the pathogenesis of postabortal peritonitis.

It is our belief that in these cases the infection reaches the peritoneum by direct bacterial extension from the parametrium or retroperitoneal tissues. Lymphangitis results in cellulitis, the overlying peritoneum becomes implicated, and eventually generalized peritonitis ensues by direct invasion. As might be expected, intermediate stages may be observed. In the majority of patients with pelvic cellulitis there is no evidence of a peritoneal involvement. In a somewhat smaller group, the peritoneum immediately overlying the inflamed broad ligament is edematous, swollen, and hyperemic, comprising the so-called "peritoneal edema of Polak."¹⁴ Immunity factors, of which little as yet is known, probably further restrict extension to the overlying peritoneum. Occasionally, as a result of greater virulence of the invading organism or of a decreased local or general immunity, a generalized peritonitis does nevertheless result. Still more rarely, a parametrial abscess may rupture directly into the peritoneal cavity.

CASE 4.—E. S., a 24-year-old bipara who was two weeks overdue, complained of pain and bleeding following the insertion of a catheter eight days before admission. Since then she had had chills, fever, and persistent vomiting. Shortly before admission the patient collapsed. Examination of the patient on admission showed her to be in shock. The abdomen was distended but soft. Vaginal examination showed a hard tender mass in the left fornix which extended to the pelvic wall. The right fornix was shortened. There was considerable induration of the rectovaginal septum. The uterus seemed to be fixed in this exudate. Death occurred on the following day. At autopsy there was 2,500 c.c. of foul smelling thin pus in the abdomen. The endometrium and placental site were dark red, necrotic, and friable. Both the tubes and ovaries were normal. Bilateral parametrial abscesses were present, the left larger than the right. On section it was demonstrated that the right parametrial abscess had ruptured into the general peritoneal cavity.

In spite of the fact that in any large series of abortions studied clinically, parametritis is a more frequent complication than salpingitis, at necropsy fatal peritonitis will most often be found to be secondary to salpingitis. The parametrium tends to localize and restrict the infection and prevent its further spread to the peritoneum. On the other hand, virulent post-abortal infection of the tubes, usually if not always, involves the peritoneum.¹⁵

3. *By Way of the Myometrium.*—Extension of infection from the endometrium to the peritoneum through the myometrium can be said to have occurred only if the tubes and parametrium appear normal and there is evident extension throughout the entire thickness of the uterine wall. This was the rarest method of infection encountered.

CASE 5.—C. M., a 21-year-old primipara, was admitted to the hospital Dec. 27, 1937, stating that after fourteen weeks of amenorrhea she had had a spontaneous abortion four days before admission, followed by lower abdominal pain, vaginal bleeding, and fever. On admission the temperature was 101° F., and the abdomen was soft and not distended. There was slight vaginal bleeding but no induration or masses in the fornices. Despite the administration of sulfanilamide, five days after admission the abdomen was distended, tender, and contained fluid. *Escherichia coli* was obtained on blood culture. Eleven days after admission indefinite masses were felt in the abdomen. Three days later, under local anesthesia, incision and drainage of the peritoneal cavity through bilateral McBurney incisions was done, and 1,000 c.c. of pus evacuated which was found on culture to contain *Esch. coli*. The patient died eight hours after operation. At autopsy there was an extensive purulent peritonitis with 1,500 c.c. of thick foul-smelling pus in the peritoneal cavity. There were multiple abscesses between the intestinal loops which were glued together by a plastic exudate and there was a large abscess underneath the liver. The uterus was somewhat enlarged, and the entire fundus was converted into a gangrenous plaque. The remainder of the endometrium was the seat of a suppurative endometritis without abscess formation. An extensive thrombophlebitis was present, involving the femoral, external iliac, hypogastric, vesical, uterovaginal, hemorrhoidal, common iliac, and renal veins. The inferior vena cava was normal. The para-

metrium, except for extensive thrombophlebitis, did not seem thickened. The tubes were normal in size and the lumina clean. The right lung had several small red infarcts and there was a thrombosis of the right pulmonary vein.

In this type of case the uterus, whole or in part, is converted into a suppurative or gangrenous plaque which on histologic study shows characteristic evidence of acute inflammation with fragmentation and necrosis of the myometrium. Although the possibility of direct emptying of the lymphatics of the uterus into the peritoneum cannot absolutely be denied, it would again seem that direct extension from the uterine musculature to the peritoneum is the most likely route of extension in this case. Occasionally a less severe suppurative process occurs and discrete abscesses are formed in the wall of the uterus varying from several millimeters to several centimeters in size, although it has been said that this lesion "is almost a curiosity." In all such cases suppurative endosalpingitis was also present and was probably the route of infection to the peritoneum.

CASE 6.—C. B., a 29-year-old primipara, stated that following six weeks of amenorrhea she spontaneously aborted two days prior to admission Nov. 8, 1938. She appeared acutely ill, with generalized peritonitis, and died four days after admission. Blood culture revealed 316 colonies of *Staphylococcus aureus* per cubic centimeter. At autopsy there was a marked plastic peritonitis throughout the general peritoneal cavity, most severe in the pelvis. The endometrium was necrotic, particularly at the placental site. The tubes showed suppurative endosalpingitis with pus in the lumina. The fimbriated ends were open. The uterus contained multiple small abscesses varying from a pinhead to a pea in size. The uterine and vaginal veins were thrombosed, although otherwise the parametrium was not thickened. There were coalescent multiple miliary abscesses of the lungs.

In addition to the pathologic changes already described, two other lesions are often encountered in association with postabortal peritonitis, namely, ovarian abscess and thrombophlebitis. An ovarian abscess may occur as a tubo-ovarian abscess or as a cortical abscess resulting from lymphatic extension to the center of the ovary,¹² or as an infection of a corpus luteum cyst by "spillage" of pus over the ovary from the peritoneum or the tube.

CASE 7.—P. J., a 17-year-old multipara, was admitted Oct. 6, 1936, with the following history: After six weeks of amenorrhea, turpentine was taken orally to induce menstruation. Five days before admission, severe lower abdominal pain, fever, vaginal bleeding, and passage of the products of conception had occurred. She had had chills for two days. The abdomen was tense, distended, and tender. On vaginal examination an indefinite soft mass with no circumferential induration was felt in each fornix. Despite intensive supportive therapy, the patient died nine days after admission. At autopsy, 2,500 c.c. of yellow, thick, foul-smelling pus was contained in the peritoneal cavity. The intestinal loops were matted together by dense adhesions. The uterus was normal in size, the endometrium gangrenous. On the right side a tubo-ovarian abscess measuring 3 by 2 by 2 cm. was found. The left tube was inflamed, thickened, and open at the fimbriated end. The mucosal lining of both tubes was gangrenous. The left ovary contained an infected corpus luteum cyst which measured 3 by 4 by 4 cm.

Thrombophlebitis of the uterine and ovarian veins is found frequently in postabortal peritonitis. It is believed that this lesion is usually secondary to infection of the parametrium or to direct extension from infected uterine sinuses. In the peritonitis cases it tends to remain localized in the pelvis and only rarely gives rise to pyogenic metastases. The reason for this is difficult to explain.

Discussion

In this series of 61 cases of postabortal peritonitis, all cases presented an endometritis of varying severity. The infection spread from the endometrium to the peritoneum as a result of direct extension through (1) the tubes, (2) the parametrium, (3) the myometrium, (4) by a combination of these routes. (Fig. 1.)

1. Direct extension through the tubes seemed to be the pathway of infection in 40, or 66 per cent, of the cases studied.

2. Extension of the infection from a parametritis to the peritoneum occurred in 6 cases, or 10 per cent. In one case the peritonitis was caused by a rupture of a broad ligament abscess into the peritoneal cavity.

3. The infection extended through the myometrium in 4, or 7 per cent, of the cases.

4. In 6 patients, endometritis, salpingitis, parametritis, and peritonitis were present. The pathway of infection was not clear.

5. In 4 patients, endometritis, abscess of the myometrium, salpingitis, and peritonitis occurred. It is probable that in this group the tubes were the chief pathways of extension as the myometrium contained discrete abscesses with no contiguous inflammation of the enveloping peritoneum. These cases are not included in the first group because of the questionable etiology of the peritonitis.

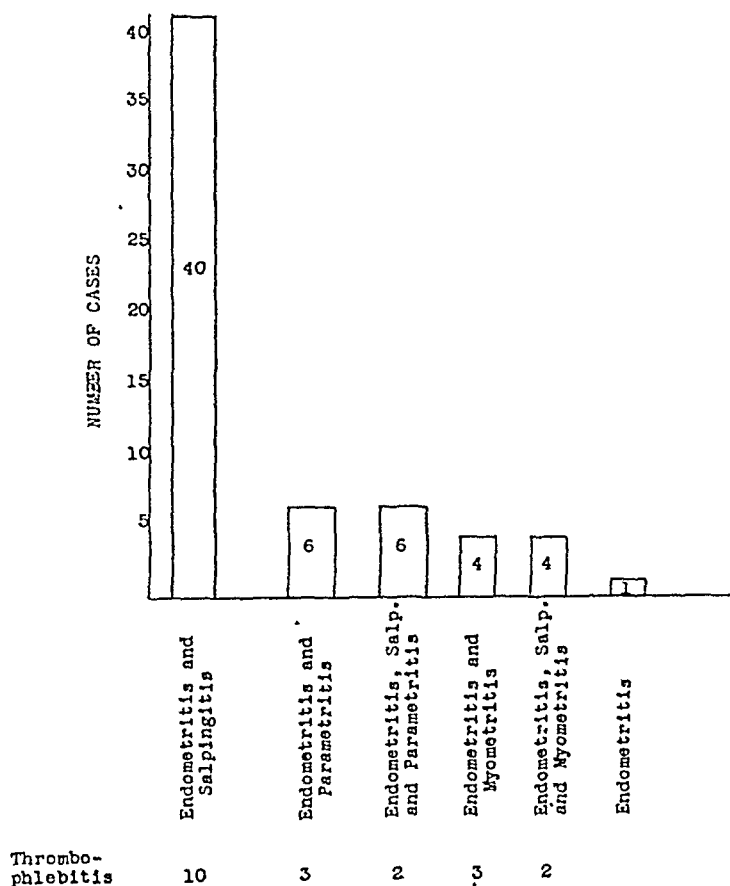


Fig. 1.—Pathogenesis of postabortal peritonitis.

Ovarian abscess was found 17 times, an incidence of 28 per cent, although no exact figure can be given as to the type of abscess present, since this data was not specifically recorded. It may occur with any mode of infection and was equally frequent with parametritis, salpingitis, or myometritis.

Thrombophlebitis of the uterine or ovarian veins, or of both, occurred in 20, or 33 per cent of all the patients observed. It was more common in the patients with parametritis or myometritis alone or in combination, than in those with salpingitis alone. Of 40 patients with salpingitis and peritonitis, 10 or one-fourth showed phlebitis, whereas in the 20 cases with parametritis, myometritis, and peritonitis, 10 showed venous inflammation. In 15 of the 20 patients there was localized thrombophlebitis. In 5, embolic abscesses of the lungs were present. No other sites of embolization were found despite careful study.

In this series the most common pathway of infection to the peritoneum was by direct extension through the tubes.

Summary

A series of 61 cases of postabortal peritonitis was studied.

The infection spread from the endometrium to the peritoneum by way of the tubes in 66 per cent, the parametrium in 10 per cent, the myometrium in 7 per cent, and in other combinations, 17 per cent.

References

1. Falk, H. C.: *Am. J. Surg.* 35: 153, 1937.
2. Williams, J. W.: *Bull. New York Acad. Med.* 7: 260, 1931.
3. Goodall, J. R.: *Puerperal Infection*, Montreal, 1932, Murray Printing Co., Ltd.
4. Halban, J., and Koehler, R.: *Die pathologische Anatomie des Puerperal-processes*, Vienna, 1919, W. Braumüller.
5. Martland, H. S.: *Am. J. Surg.* 26: 90, 1934.
6. Watson, B. P.: *AM. J. OBST. & GYNEC.* 16: 157, 1928.
7. Watson, B. P.: *Puerperal Sepsis and Thrombophlebitis*, in Curtis: *Obstetrics and Gynecology*, Philadelphia, 1933, W. B. Saunders Co., Vol. II.
8. Wislacki, G. B., and Dempsey, E. W.: *Anat. Rec.* 75: 341, 1939.
9. Falk, H. C.: *Practical Clinical Gynecology*, *Am. J. Surg.* 39: 185, 1938.
10. Hofbauer, J.: *Bull. Johns Hopkins Hosp.* 38: 255, 1936.
11. Hertzler, A. E.: *Diseases of the Peritoneum*, Philadelphia, 1930, W. B. Saunders Co.
12. Rouvière, H.: *Anatomy of the Human Lymphatic System*, Ann Arbor, 1938, Edwards Brothers, Inc.
13. Cullen, T. S.: *Cancer of the Uterus*, Philadelphia, 1909, W. B. Saunders Co.
14. Polak, J. O.: *Pelvic Inflammation in Women*, New York, 1931, D. Appleton-Century Co.
15. Frankel, O.: Personal communication.

STUDIES CONCERNING MORBIDITY AND MORTALITY FOLLOWING HYSTERECTOMY

JOSEPH H. PHILLIPS, M.D., BROOKLINE, MASS.

(From *The Free Hospital for Women*)

ALTHOUGH during the past decade a voluminous literature has accumulated concerning various problems associated with hysterectomy, comparatively few reports have been compiled with studies on morbidity and mortality. Presumably, one of the obstacles has been that we have no morbidity standard in gynecology which might permit uniform interpretation of the various factors. It is, therefore, of interest to investigate the incidence and etiology of morbidity and mortality in a gynecological clinic where the resident staff under supervision did 33 per cent of the operations. Furthermore, we believe that the publication of the findings will be of value to others for comparative study.

Materials and Methods

This study is based on a series of 980 consecutive hysterectomies performed during a twenty-six-month period, from Jan. 1, 1942, to Feb. 29, 1944. We had no particular reason for selecting this group other than to study the latest series over a two-year period and yet have a sufficient number. There were 643 complete, 253 subtotal, and 84 vaginal hysterectomies. These figures include both private and ward, white and Negro patients, operated upon by thirteen attending surgeons and sixteen members of the resident staff

TABLE I. TYPES OF HYSTERECTOMY AND OPERATORS

TYPE OF HYSTEREC- TOMY	VISITING SURGEON		RESIDENT STAFF		AVERAGE AGE (YEARS)	AVERAGE HOS- PITAL DAYS	TOTAL NUM- BER	PER CENT
	NUMBER	PER CENT	NUMBER	PER CENT				
Complete	435	67.4	208	32.6	43.6	13.1	643	65.6
Subtotal	185	73.1	68	26.9	40.7	13.3	253	25.8
Vaginal	50	59.5	34	40.5	53.9	16.3	84	8.6

(Table I). Operations performed by the latter were done under the supervision of an attending surgeon or the senior resident.

The indications for hysterectomy as well as the operative technique were uniformly followed by all. We made no attempt to grade the operative procedure according to the technical difficulties encountered in each case, since we observed that morbidity and mortality in this series did not depend on them. It was noted that after a very simple operation, a patient may suffer from hazardous complications, while after an extensive Wertheim procedure, another may have an uneventful convalescence. However, there is no doubt that over a long period of time and in an extensive series of cases technical difficulties do affect convalescence.

The interpretation of the various factors and the conclusion reached that the patient was morbid were based on an elevated temperature, rise in pulse rate, white cell counts, urinalysis, x-ray findings, and physical examination. No attempt was made to separate the white from Negro patients, as the latter comprised an insignificant number in this series. The postoperative course of these was not different from the white patients.

Pathologic and General Findings

Table II shows the pathology encountered in the series. It is of interest that 472 patients, or 48.1 per cent, were operated upon because of leiomyomas producing symptoms requiring surgical intervention. Among these, 120 were complicated by bilateral chronic salpingo-oophoritis. Twelve per cent, or 118 patients, were operated upon for chronic bilateral salpingo-oophoritis. Procidentia was present in 115 patients or 11.7 per cent. Vaginal hysterectomy was done in 84 of this group, and none of these was complicated by other pelvic pathology except cystocele, rectocele, or both. The miscellaneous group includes patients with functional flowing and endometrial hyperplasia, chronic cervicitis with hypertrophy, badly lacerated cervix with persistent vaginal discharge, and chronic endometritis and myometritis. These accounted for 68 operations or 6.9 per cent of the series. Various degrees of adenomyosis was found on microscopic examination in 197 patients or 20 per cent. Malignancy of the cervix, endometrium, or ovaries was present in 79 cases or 8 per cent. Of these, 49 had adenocarcinoma of the endometrium, ten of which, or 20.4 per cent, were complicated by leiomyomas. Although tuberculous salpingitis has an incidence of about 5 per cent of all inflammatory processes of the tubes (Curtis, 1942),¹ only 9 cases or 0.9 per cent were found in this group. If we had calculated the percentage on the basis of the number of patients examined to find these, it would be insignificantly small, as in all the

TABLE II. PATHOLOGY PRESENT

PATHOLOGY	HYSTERECTOMY		
	COMPLETE	SUPRAVAGINAL	VAGINAL
Leiomyomas	333	139	0
Chronic salpingo-oophoritis	77	41	0
Miscellaneous	51	17	0
Adenocarcinoma of the endometrium	49	0	0
Procidentia	29	2	84
Benign ovarian growths	23	10	0
Endometriosis (pelvic)	21	25	0
Carcinoma of the cervix	16	0	0
Endometrial polyps	16	8	0
Chronic endometritis	14	1	0
Tuberculous endometritis and salpingitis	7	2	0
Other malignancies of the uterus	4	1	0
Carcinoma of ovaries	2	7	0
Bicornute uterus	1	0	0
Total	643	253	84

patients except one the diagnosis was made before operation in the sterility clinic on the basis of tuberculous endometritis.

Table III lists the number of patients who had had previous abdominal operations and the additional procedures carried out along with hysterectomy. Most of the previous operations had been on the pelvic organs, but some had been cholecystectomies, appendectomies, and bowel operations. There was no increase in morbidity in patients who had had previous operations. In some, extensive omental and bowel adhesions were present which made the hysterectomy more difficult, but did not excessively prolong the procedure. Previous ventral uterine fixations, Caesarean sections, and suspensions presented no problem. In fact, we have the distinct impression that patients who have had previous abdominal operations do as well or better than fresh cases.

TABLE III. PREVIOUS OPERATION AND OTHER PROCEDURES WITH HYSTERECTOMY

PROCEDURES	HYSTERECTOMY					
	COMPLETE		SUPRAVAGINAL		VAGINAL	
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
Previous abdominal operations	253	39.3	102	40.3	10	11.9
Salpingo-oophorectomy	629	97.6	250	98.4	0	0
Vaginal plastic	73	11.3	12	4.7	77	91.6
Appendectomy	376	58.4	116	45.8	0	0

Bilateral or unilateral salpingo-oophorectomy was done in 629 patients or 97.6 per cent of those undergoing complete hysterectomy, and in 250 patients or 98.4 per cent of those undergoing the supravaginal operation. It has been a general rule in this clinic to remove both ovaries and tubes in patients over 45 years of age, if hysterectomy were indicated. This procedure was followed in most of the patients with chronic pelvic inflammation, regardless of age, if the uterus were removed. This presumably has avoided occasional secondary operation, since cyst formation in the remaining ovary occurs in patients who have had chronic pelvic inflammation.

Anterior colporrhaphy, colpoperineorrhaphy, or both, were done on 73, or 11.3 per cent, of those having complete hysterectomies, and on 12, or 4.7 per cent, of those having subtotal operations. These procedures were done on 77, or 91.6 per cent, of the vaginal hysterectomy group. These additional operations did not increase the morbidity in the complete and subtotal hysterectomy groups, but in the vaginal hysterectomy series, it was noted that the more extensive the plastic operation, the more frequent were the complications. This was particularly striking in patients with large rectocele and enterocele which are commonly present with procidentia.

Appendectomy was done routinely in all abdominal operations, except in a rare case, where the appendix was grossly normal, obviously atrophied, difficult to expose, or could not be removed without excessively prolonging the operation. Phenol-alcohol or cautery technique was used routinely. The appendiceal stump was left exposed in most; in some it was buried with a figure-of-eight suture. Appendectomy did not influence the morbidity in this series. It is interesting that in 152, or 30.9 per cent, of the routine appendectomies, the appendix was found on microscopic examination to be chronically inflamed, and possibly a potential menace.

Causes of Morbidity

Table IV shows the causes of morbidity which were established as etiology of elevated temperature and rise in pulse rate in three types of hysterectomy. Pelvic peritonitis and parametritis were responsible for almost half of the morbidity in the vaginal hysterectomy group, and occurred more frequently in the subtotal than in the complete hysterectomy series. Extensive plastic procedures with vaginal hysterectomy and opening of the peritoneal cavity in a contaminated field were likely responsible. In septic cases, ineffective drainage through the narrow lumen of the remaining cervix in supravaginal hysterectomy patients contributed to extension of sepsis and prolonged elevated temperature. If sepsis should occur in those who had complete hysterectomy, ample room is provided by the wide vaginal cuff for immediate drainage and localization of the process. Cauterization of the cervix, too, creates a nidus of necrotic tissue ideal for the origin of sepsis. In this series pelvic peritonitis and parametritis occurred three times as often in the subtotal as in the complete hysterectomy group.

There were no bladder, ureteral, or bowel injuries in the entire series. Cystitis occurred more often after the subtotal hysterectomy, but its incidence in the entire series was remarkably low. Pyelitis, too, was rare. The administration of sulfonamides rou-

TABLE IV. CAUSES OF MORBIDITY

COMPLICATION	HYSTERECTOMY					
	COMPLETE		SUPRAVAGINAL		VAGINAL	
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
Femoral phlebitis	12	1.8	3	1.1	0	0
Cystitis	9	1.4	4	1.5	2	2.3
Abdominal wound sepsis	8	1.2	7	2.7	0	0
Pelvic peritonitis	6	0.9	7	2.7	38	45.2
Postoperative hemorrhage (vaginal)	5	0.7	0	0	2	2.3
Lobar pneumonia	4	0.6	0	0	0	0
Pulmonary atelectasis	4	0.6	2	0.7	0	0
Hematoma of wound	3	0.4	2	0.7	0	0
Pulmonary infarct	3	0.4	1	0.3	0	0
Psychosis	3	0.4	0	0	1	1.1
Superficial phlebitis	3	0.4	2	0.7	0	0
Pyelitis	2	0.3	0	0	0	0
Mechanical intestinal obstruction	1	0.1	0	0	1	1.1
Paralytic ileus	0	0	0	0	1	1.1
Atypical pneumonia	1	0.1	0	0	0	0
Unknown	122	19.8	53	20.9	0	0

tinely to all patients with inlying urethral catheters, undoubtedly had a prophylactic effect. On the other hand, deep femoral phlebitis was noted more often after complete hysterectomy. It occurred in 12 patients, or 1.8 per cent. Only 3 patients, or 1.1 per cent, of the subtotal group developed this complication. Likewise, postoperative hemorrhage occurred in 5 patients, or 0.7 per cent, undergoing complete hysterectomy, but none in those who had the subtotal operation.

The remainder of Table IV shows a small number of various complications from which nothing definite can be drawn, except that they do occur incidentally with other abdominal operations. However, there were 122 patients, or 19.8 per cent, of the complete, and 53 patients, or 20.9 per cent, of the subtotal hysterectomy groups, who had an elevated temperature and pulse rate for the first two to four days postoperatively, but whose hospital stay was not prolonged and the temperature and pulse were normal on the usual day of discharge from the hospital. We could not find any cause for the elevated temperature and pulse. Minimal pulmonary atelectasis and low-grade pelvic sepsis, which could not be recognized clinically, might possibly have been the cause. This group presents a challenge to any morbidity standard which one might establish for hysterectomy.

Mortality

Table V lists the causes and incidence of mortality. No deaths occurred in the subtotal hysterectomy group. There were three deaths in the complete, and one in the vaginal hysterectomy group, respectively. This gives complete hysterectomy a mortality rate of 0.46 per cent and vaginal hysterectomy a rate of 1.1 per cent. The rate for the entire series is 0.40 per cent.

Two deaths occurring after complete hysterectomy were in debilitated patients with advanced adenocarcinoma of the fundus, and one was in a young patient with pelvic endometriosis who developed postoperative hemorrhage and peritonitis. Of the four deaths occurring in this series, three were in patients operated upon by the visiting surgeons, and one by the resident staff (Table V).

TABLE V. MORTALITY

PATIENT NUMBER	AGE	PATHOLOGY	CAUSE	OPERATOR
<i>Complete Hysterectomy—3 Deaths</i>			<i>Mortality Rate—0.46 Per Cent</i>	
1	69	Adenocarcinoma of the fundus	Lobar pneumonia and paralytic ileus	Staff surgeon
2	68	Adenocarcinoma of the fundus	Acute coronary occlusion	Staff surgeon
3	35	Pelvic endometriosis	Hemorrhage and peritonitis	Staff surgeon
<i>Vaginal Hysterectomy—1 Death</i>			<i>Mortality Rate—1.1 Per Cent</i>	
1	38	Procidencia	Hemorrhage and peritonitis	Asst. resident

Discussion

The review of the literature on morbidity after hysterectomy reveals that many factors are involved and that no morbidity standard is suitable for this operation. Some authors (Danforth, 1943,² Jones and Doyle, 1943³) used the obstetric standard, but found it inadequate. We also find that it is difficult to apply any standard which could be used by all for a comparative study. In a study of any series of operations, it may be readily seen that a variety of complications may arise which are not inherent in the procedure but may be the sequelae of the simplest operation. It is difficult to define prerequisites as to what constitutes morbidity in a given patient. Numerous factors are involved. Some complications depend on the individual patient; her age, pathology encountered, and diseases remote from the surgical procedure. Others may depend on the ability and experience of the surgeon as well as on the procedure he chooses (Bartlett and Simmons, 1932,⁴ Dupertius and Zollinger, 1938,⁵ Smith, 1940⁶). We believe, however, that much may be accomplished if the incidence of various complications is reported by a large number of observers from several clinics. From comparative studies of these reports certain generalizations might be formed and attention focused upon the etiology of morbidity and its incidence reduced.

In this study we made every effort to account for each complication and, therefore, reviewed all the factors pertaining to the individual case. It was noted that in this series deep femoral phlebitis occurred only in patients over 35 years of age, and was also more frequent after complete hysterectomy. Age also was noted to influence the incidence of morbidity which was more frequent in those over 45 years. Operations on patients with benign chronic pathologic conditions were followed by a low incidence of morbidity, but patients with malignant growths of the uterus or the adnexa suffered from frequent complications. Two of the four deaths in this series were in patients with adenocarcinoma of the endometrium. To be sure, both were over 65 years of age and poor risks, but others in this age group with benign conditions tolerated similar procedures well. Abdominal wound sepsis and poor healing of tissues are frequent with malignancies.

Although it is not the purpose of this paper to enter into the much discussed question of whether complete or subtotal hysterectomy should be done routinely, we are in complete agreement with other observers (Bryan and Traube, 1936,⁷ Masson, 1927⁸ and 1940,⁹ McKibbin and Counsellor, 1942¹⁰) that complete hysterectomy is by far the better procedure. The main advantage of the total operation is that the cervix, as the possible future site of infection or malignancy, is removed, and conization or cauterization is hardly of any value as compared with complete removal. We have not noted any shortening or prolapse of the vagina following a complete hysterectomy, neither have the patients complained of a dry vagina as in contrast to complaints of leucorrhoea after the subtotal operation. In this series, 65.6 per cent were complete, 25.8 per cent were subtotal, and 8.6 per cent were vaginal hysterectomies respectively. Postoperative complications were present in 9.9 per cent of the complete, 11 per cent of the subtotal, and 53.1 per cent of the vaginal hysterectomies.

The average hospital stay was 13.1 days for the complete, 13.3 days for the subtotal, and 16.3 days for the vaginal hysterectomy.

It is of interest that the highest morbidity and mortality and the longest hospitalization were in the vaginal hysterectomy group. Undoubtedly, this

was due to the extensive plastic procedures and opening of the peritoneum which routinely accompanied the operation, for all these patients had procidentia with cystocele, rectocele, and enterocele. Also the average age of these was 53.9 years in comparison with an average of 43.6 years for the complete, and 40.7 years for the subtotal hysterectomy patients. Danforth, 1943,² reported a series of 517 consecutive vaginal hysterectomies with a morbidity rate of 42.1 per cent. There was no mortality. Masson, 1940,⁹ reported 607 cases from the Mayo Clinic over a five-year period with a mortality rate of 1.5 per cent. However, the morbidity was not reported, but in an earlier paper (Masson, 1937¹¹) he states that, after vaginal hysterectomy, patients averaged 18.4 hospital days, in contrast to 16.5 days for those who had an abdominal total hysterectomy. In this series the morbidity rate of the vaginal hysterectomy was 53.1 per cent and the mortality rate 1.1 per cent, both exceeding those after the abdominal operation. The late results were also inferior to the combined abdominal and plastic procedure for procidentia. Although the end results were satisfactory for this age group, the vagina was markedly shortened in 15 patients or 17.8 per cent; one developed complete prolapse of the vagina; and 16 patients, or 19 per cent, had recurrent cystocele or enterocele. However, secondary plastic operations were performed on the latter without morbidity or mortality. The results in this small group are not intended to condemn the procedure, which has its indications, but, with limitation.

One-third of all the operations in this series was done by the resident staff under the supervision of the visiting surgeon or the senior resident. It is of interest that only one death occurred in this group (Table V). To be sure, these patients were selected, and the visiting surgeons operated upon all the poor risk cases, but this did not exclude the operations which were technically difficult to perform.

Summary

1. A study of the causes of morbidity and mortality in 980 patients following hysterectomy is presented.

2. The morbidity rate for the supravaginal hysterectomy was higher than that for the total hysterectomy; and for the vaginal operation it was 53.1 per cent.

3. The incidence of cystitis and pyelitis has been reduced to 3 per cent by the prophylactic use of sulfonamides.

4. The mortality rate for the entire series was 0.4 per cent.

5. The resident staff under supervision performed 33 per cent of the operations with a mortality rate of 0.32 per cent.

References

1. Curtis, A. H.: *A Textbook of Gynecology*, ed. 4, Philadelphia, 1942, W. B. Saunders Co., p. 217.
2. Danforth, W. C.: *Surg., Gynec. & Obst.* 76: 411, 1943.
3. Jones, H. O., and Doyle, L. W.: *AM. J. OBST. & GYNEC.* 46: 60, 1943.
4. Bartlett, M. K., and Simmons, R. A.: *Surg., Gynec. & Obst.* 55: 777, 1932.
5. Dupertius, S. M., and Zollinger, R.: *Surg., Gynec. & Obst.* 67: 689, 1938.
6. Smith, P. H.: *AM. J. OBST. & GYNEC.* 40: 118, 1940.
7. Bryan, W. A., and Traube, C. C.: *Ann. Surg.* 103: 914, 1936.
8. Masson, J. C.: *AM. J. OBST. & GYNEC.* 14: 486, 1927.
9. Masson, J. C.: *AM. J. OBST. & GYNEC.* 48: 255, 1940.
10. McKinnon, D. A., and Counsellor, V. S.: *Surg., Gynec. & Obst.* 74: 957, 1942.
11. Masson, J. C.: *S. Clin. North America* 17: 1131, 1937.

FIVE YEARS' EXPERIENCE WITH CAUDAL ANESTHESIA IN PRIVATE OBSTETRIC PRACTICE

ARTHUR BAPTISTI, JR., B.S., M.D., F.A.C.S., HAGERSTOWN, MD.

IN JULY, 1944, in a published commentary,¹ I called attention to the fact that the administration of an anesthetic agent into the caudal canal is never risk free. I indicated that the use of an indwelling needle or catheter in the caudal canal increases the possible complications, and, more particularly, I attempted to point out that caudal anesthesia has an inherent tendency to arrest the progress of normal labor. Thus, even though the risk of caudal anesthesia may be minimized to the point of negligibility, its administration before the terminal stage of labor constitutes unsound obstetrics. These conclusions were based on a reasonably broad experience with caudal anesthesia in a large obstetric clinic during the years 1938 and 1939.²

Following the publication of the commentary I received a large number of personal communications from obstetricians throughout the country. These letters were expressions of men who shared my conviction that the propagandists who were promoting continuous caudal analgesia were advocating unsound, unsafe obstetrics. The great majority of these personal communications contained an inquiry concerning my opinion of single injection, terminal caudal anesthesia, and asked if and when I use it. This present report concerns my experience with single injection, terminal caudal anesthesia for delivery during the five years that I have been in private practice. Most of this practice is done in the Washington County Hospital, Hagerstown, Maryland, an institution of about 175-bed capacity, where there are no resident house officers and no service cases. A small part of the practice is done as consultations in several smaller hospitals in surrounding counties. Under such circumstances any procedure used in private obstetric practice must be not only safe but simple and free from complications.

Practically all primigravidas are delivered by elective outlet forceps with median perineotomy and repair. Many multiparas are delivered by outlet forceps with or without perineotomy, as indicated. Such a routine calls for some type of anesthesia for delivery and repair. Since there are no house physicians, any general anesthetic must be administered by a private medical practitioner or a general duty graduate nurse, untrained in anesthesia. For the past five years I have used single injection caudal anesthesia for delivery and repair in selected cases, and over this period of time I have used it with increasing frequency. During the past several years the local doctor shortage has made it necessary to depend upon an anesthetic procedure which can be carried out by oneself. This fact, plus the fact that the procedure, in my hands, has been completely satisfactory, free from complications and enthusiastically received by the patients, accounts for my increasingly frequent use of terminal caudal anesthesia. However, I do not attempt to use the procedure in every patient delivered. Some patients are psychologically unsuited for regional anesthesia; in others, labor progresses so rapidly that the procedure is unnecessary and impracticable; in others, there is sufficient subcutaneous fat over the sacrum to prevent identification of the sacral hiatus by palpation and the procedure is not attempted. If caudal anesthesia is at-

tempted, and the needle does not definitely enter the sacral canal, no fluid is injected. This fact can be verified by a sign which I reported in 1939;² that is, the tip of the needle can be felt to impinge on the anterior surface of the posterior sacral wall after it has entered the sacral canal.

My records reveal that in the five years from August, 1939, to August, 1944, 318 obstetric cases have been delivered under caudal anesthesia and seen for the routine six weeks' postpartum checkup examination. Forty-five of the total represent obstetric complications such as breech presentations, transverse arrests, etc., in which procedures other than outlet forceps deliveries were done. Many of these were seen in consultation. In every case but one, anesthesia was excellent and no supplementary anesthetic was required. In one case (occiput directly posterior and prolonged, arrested second stage) unilateral anesthesia only was obtained and inhalation anesthesia was necessary. One cesarean section was done in this group of 45 with no supplementary anesthesia necessary. However, in my opinion, caudal anesthesia for cesarean section is hazardous because the solution must be driven higher than usual to get a satisfactory anesthesia and this carries an increased risk of vascular collapse.

The remaining 273 cases represent normal obstetric patients who were delivered under caudal anesthesia by elective outlet forceps. The group represents only 243 individuals, as 30 patients were delivered in consecutive pregnancies. Two hundred ten of this group were primigravidas and perineotomy was done in every one. Thirty of the multiparas had perineotomy. In this elective outlet forceps group, supplementary anesthesia was necessary in only one case, which developed unilateral anesthesia only. In this case, local infiltration anesthesia was used on the unanesthetized side.

This total group of 318 cases, in which caudal anesthesia was entirely satisfactory in 316, represents an attempt to administer caudal anesthesia to 320 cases. In two attempted cases the caudal canal could not be entered although it seemed clearly palpable. No solution was injected in these two cases.

In the total group of 318 cases there was no maternal mortality and no complication from the anesthetic, either maternal or fetal. One stillborn fetus was delivered by breech extraction after a prolonged second-stage labor, the baby having died in utero before the patient was seen in consultation. One other baby died four days post partum from erythroblastosis. All other babies were born in excellent condition. Caudal anesthesia is a tremendous advantage to the prematurely delivered infant.

In the first 145 cases in this series, 1 per cent novocain was used as the anesthetic agent, and in the last 173 cases 1.5 per cent metycaine was used. I prefer metycaine because of its rapid and prolonged action. Thirty cubic centimeters of metycaine solution will usually produce complete caudal anesthesia for one hour. Its action may be prolonged by the addition of adrenalin but more prolonged action is not necessary for the usual delivery and repair. Metycaine may produce a very mild general systemic reaction which patients describe as lightheadedness and generalized tingling. Vomiting occasionally occurs if the solution is injected too rapidly. These reactions, if they occur, are fleeting and are often followed by a mild euphoria when patients frequently say, "I feel wonderful."

Technique

The technique used today is slightly modified from that advocated in 1939.² The modifications are pointed toward safety and comfort during administration. No special

equipment is necessary. The sterile pack contains one each of the following: small towel; 3 inch, 19 gauge spinal puncture needle; small hypodermic needle; 10 c.c. syringe; 150 c.c. Pyrex basin; ampule containing 5 c.c. of 20 per cent metycaine with file for opening; and several gauze sponges.

The sterile pack is opened on a utility table and the operator dons sterile gloves. The 20 per cent metycaine is transferred from the ampule to the Pyrex basin and the utility nurse dilutes this with 60 c.c. of sterile normal saline solution (the flasks of saline contain this measured amount before autoclaving). The resulting mixture represents 1.5 per cent metycaine solution. While the operator is mixing the solution, the nurse cleans a wide area of skin overlying the sacral hiatus with iodine followed by alcohol. During this skin sterilization, the patient (now in hard labor) lies on her left side with the knees flexed. With the patient still on her side, the operator infiltrates the skin and subcutaneous tissue overlying the hiatus with several cubic centimeters of metycaine solution, using the 10 c.c. syringe and hypodermic needle. The skin weal is pressed away with the finger. Following the next painful uterine contraction the patient is placed in the knee-elbow position with the back horizontal, and the towel is placed over the patient's back so that the operator can palpate the midline of the back through the towel. This maneuver helps considerably in directing the needle into the sacral canal. The exact location of the hiatus is identified, and the 19 gauge needle with stylet is inserted through the hiatus into the canal. The needle is then introduced almost up to the hub. During this penetration it is important to keep the direction in the midline and it is also important to moderately depress the hub of the needle so that the tip of the needle travels close to the anterior surface of the posterior sacral wall. When the needle has penetrated to most of its length, its tip will meet the curving sacral wall and can be felt to impinge against it. This sign definitely verifies the presence of the needle in the caudal canal. Keeping the tip of the needle close to the posterior sacral wall also acts as a safeguard against the accidental penetration of a low-lying dural sac. The stylet is then removed, the 10 c.c. syringe attached to the needle and the plunger withdrawn. If spinal fluid is withdrawn, the procedure is abandoned. This happened twice in my early experience with caudal anesthesia but it has not happened since I have been careful to keep the needle close to the posterior sacral wall. Frequently a drop or two of blood will be aspirated into the syringe but this may be safely ignored so long as there is no steady flow indicating that the needle lies intravascular. The syringe is then removed and filled with 10 c.c. of metycaine solution which is injected slowly through the needle under only moderate pressure. The patient is kept in the knee-elbow position to this point in the procedure. The syringe is now detached from the needle and the patient placed on her left side again with the knees flexed and the needle remaining in the caudal canal. Several minutes are allowed to elapse during which time the nurse constantly palpates the radial artery and checks the patient's pulse. Any accident from the injection will be manifested first by a rapid, weakening pulse. So long as the pulse remains normal, one may feel sure there are no complications and it is absolutely necessary to impress this fact upon every delivery room nurse. After several minutes observation the patient is requested to move her toes. If she can move her toes and there is no sensation of numbness, another 10 c.c. of metycaine are injected after aspiration reveals no fluid. The patient should feel no sensory changes in the feet several minutes after the first 10 c.c. have been introduced. If she does, it is wise to defer the second 10 c.c. and look for motor weakness in the legs, which would suggest intradural injection although this would be very unlikely after the previous precautions. However, it is advisable to be overcautious with caudal anesthesia. Several more minutes are allowed to elapse after the second injection, when a third 10 c.c. are injected after a negative aspiration test. Following this final 10 c.c. injection, the needle is immediately withdrawn and the patient placed flat on her back. The patient has been having painful uterine contractions during the administration but by the time she is turned on her back the pains are somewhat dull. She is usually conscious of one or two contractions after being placed on her back but this discomfort is usually confined to a small area immediately above the symphysis pubis. Contractions continue thereafter painlessly and typical caudal anesthesia develops completely, ten minutes or so following relief from contraction pain. Anesthesia lasts approximately one hour, which is more than enough time to drape the patient and carry out the delivery and repair.

Many patients may be kept on their side for the insertion of the needle and the injection of the entire 30 c.c. of solution, but I prefer the knee-elbow position for the initial part of the procedure for two reasons: First, I find it easier to insert the needle properly and quickly in this position. Second, I think unilateral anesthesia is less likely

to develop if the first 10 c.c. are injected in the knee-elbow position. To the uninitiated it will seem an awkward position for the patient, but the fact is that the needle insertion and the original injection can usually be accomplished between two contractions so that the patient experiences no discomfort while in this position.

Time of Administration

Although a few multiparas and the occasional primigravida may be delivered spontaneously under caudal anesthesia, its field of greatest usefulness is that of operative delivery. The practice of elective outlet forceps delivery with perineotomy is not endorsed by all obstetricians but the defense of such a routine is beyond the scope of this communication. However, it must be emphasized that the obstetrician who does not do elective forceps deliveries cannot use caudal anesthesia. The self-styled specialist who practices on the fringe of the specialty should not do elective forceps or use caudal anesthesia. If he does, both he and his patients will, soon or later, regret it.

Most of my patients are given a combination of heroin and hyoscine, hypodermically, as an analgesic before the terminal stage of labor is reached. In general, when the head has reached the perineal floor and the cervix is fully dilated, the caudal anesthesia is administered. In certain cases the anesthetic may be given before this stage is reached. Under certain conditions caudal anesthesia will markedly accelerate the latter part of the first stage of labor. If the patient is in hard labor and the head is deep in the pelvis, if the cervix is at least 5 cm. dilated and thin and if the membranes are ruptured, the cervix will often disappear and retract within a few minutes after the administration of caudal anesthesia. It is absolutely essential that the above conditions be present before caudal anesthesia can be expected to bring about this rapid cervical dilatation and completion of descent. When caudal anesthesia is administered in one 30 c.c. dose, as described above, to a patient in which the conditions just enumerated are present, her total labor is definitely shortened. I frequently use caudal anesthesia under these conditions with very gratifying results, particularly in multiparas. This practice must not be confused with the practice of administering caudal anesthesia promiscuously under any circumstances or at any stage of labor, primarily to relieve the pains of labor, as advocated by the promoters of continuous caudal analgesia.

Conclusions

The advantages, risks, and limitations of caudal anesthesia in obstetrics were pointed out in 1939.² Since that report, the advantages of the principle have been widely publicized in both scientific and lay journals so that there is no need to resummairize them. Unfortunately, the "moonshees,"* in their recent prolific publications, have either failed to recognize or failed to divulge the limitations of the principle. Such uncritical, overenthusiastic reporting naturally met with resentment in the trained and sage obstetric world. However, it must be recognized that under certain conditions caudal anesthesia is useful and should be an integral part of the armamentarium of the obstetrician who knows when to use it and when not to use it.

The employment of any procedure in private practice without trained assistance is an accurate criterion of its practicability. The present report reveals my experience with terminal caudal anesthesia attempted in 320 cases. In two cases administration was abandoned because the caudal space could not be penetrated. In two other cases supplementary anesthesia was necessary. In the 316 cases remaining, the procedure was completely satisfactory with no maternal or fetal complications. This series does not represent my initial experience with caudal anesthesia. In my earlier experience the percentage of failures was significantly higher, indicating that the administration is technically difficult and that practice and experience are essential for satisfactory results. However, I know that any other obstetrician can attain the same

*See Webster's New International Dictionary, Second Edition.

gratifying results. The only requisites are that he have patience and that he be a trained obstetrician. The obstetrician can master the technique of caudal anesthesia in a comparatively short time, but the anesthetist cannot become an obstetrician in that same short time.

References

1. Baptisti, A., Jr.: AM. J. OBST. & GYNEC. 48: 103, 1944.
2. Baptisti, A., Jr.: AM. J. OBST. & GYNEC. 38: 642, 1939.

A QUADRIOVULAR QUADRUPLLET PREGNANCY*

B. P. WATSON, M.D. (EDIN.), F.R.C.S. (EDIN.), F.A.C.S., F.R.C.O.G.
NEW YORK, N. Y.

(From the Sloane Hospital for Women)

THE exact incidence of quadruplet pregnancy is variously stated according to the method adopted in trying to arrive at it. Heslin suggested that it is determined by the following ratio: twins occur 1 in 80 births, triplets 1 in 80² (which is one in 6400 births), and quadruplets 1 in 80³ (which is one in 522,000 births).

In a five-year period, 1924 to 1928, Hernstein and Pflatz found a ratio of 1 in 783,041 births in Germany. The Statistical Bulletin of the Metropolitan Life Insurance Company for May, 1944, quotes figures which show that the incidence of quadruplet births in the United States for the years 1933 to 1941 inclusive was 1 in 502,230 births. I am informed by Mr. Duffield, Director, Bureau of Records and Statistics, that there is no record of the birth of quadruplets in New York City prior to the present one. Their occurrence is thus of sufficient rarity as to justify the presentation of an individual case.

The Mother.—The mother was first seen by me in June, 1943. She was then 27 years of age; she had one child, a boy, 5½ years of age. She had had one other pregnancy which ended in early abortion in 1941. There was no febrile reaction following this but she had not felt well since. Her principal complaint was more or less constant pain in the lower abdomen, which became greatly aggravated ten or twelve days following menstruation. This pain continued until the onset of the next period, at which time it became still more severe and was present on both sides. The pain was so incapacitating that she could not continue her occupation as a dancer and was forced to stay in bed for the first two days of menstruation. The menstrual periods occurred regularly every twenty-four days and lasted for five or six days.

There was no history of multiple births in her family.

In general physique the patient was 5 feet 5 inches in height, small and slender, weighing 118 pounds. General examination of cardiac, respiratory, and excretory systems was entirely negative. Pelvic examination revealed a good pelvic floor, deep vagina, parous, noncatarrhal cervix, directed downward and backward. The uterus was anteverted, freely mobile, slightly above average in size, and rather firm in consistence. Both ovaries were easily palpable, freely mobile, firm in consistence, not enlarged but more sensitive than usual. No nodulation suggestive of endometriosis could be felt through any of the vaginal fornices.

Patient had consulted several doctors for relief of her pain and had been treated with all sorts of sedatives and practically every known hormone without benefit.

After seeing and examining her I made the following note: "It is difficult to account for the pain unless on the basis of sclerosis of the ovaries, affecting ovulation and corpus luteum formation, or, possibly, of adenomyosis of the uterus. The only operative treatment one could suggest would be presacral sympathectomy or possibly hysterectomy. Advised against either of these until she has given herself the chance of at least one more pregnancy." It is interesting to note that in the six months following the delivery

*Presented before the New York Obstetrical Society, Nov. 14, 1944.

of the quadruplets the patient has experienced the same type of pain, though in much lesser degree. It now diminishes as menstruation approaches and is only slight during the actual period. Is it possible that this pain, beginning at the time of ovulation, is indicative of the ripening and rupture of multiple follicles and its continuation to the formation of multiple corpora lutea with the threat, or hope, of further multiple pregnancies if opportunity offers?

In any case, the patient took my advice for, on Nov. 2, 1943, she reported that her last menstrual period had been on July 24 and that she was pregnant.

The Pregnancy.—Last menstrual period began July 24, 1943, and the calculated date of delivery was April 31, 1944. The actual date of delivery was March 29, 1944.

When seen on November 2, which was fourteen and one-half weeks after her last menstruation, she gave a history of having had slight spotting of blood at the fifth week and intermittent brownish discharge until the middle of October. She had had intermittent abdominal pain for the past two months.

Examination showed a soft, rounded, fluctuant swelling reaching to the umbilicus. *No fetal heart sounds could be heard; no ballottement could be elicited. The cervix was soft and situated high in the pelvis.*

On November 8, when she was just over fifteen weeks pregnant, my note was as follows: "Uterus to above umbilicus; evidently contains a great deal of fluid as it is quite fluctuant. Uterine souffle is heard but no fetal heart sounds. No ballottement obtained. There is certainly hydramnios and probably a multiple pregnancy."

On November 19 her weight was 133 pounds. Blood pressure was 110/70. The uterus rose to halfway between umbilicus and ensiform cartilage, and she was very uncomfortable.

The enlargement and discomfort increased, making it difficult for her to attend to her household duties, so on December 7 she was admitted to the hospital to rest for a few days. She was then four and one-half months pregnant and the abdomen was as large as with a normal term pregnancy. An x-ray taken at this time showed "the skeletal structures of at least four feti" (Figs. 1 and 2). Fetal heart sounds could now be heard.

She returned home but had to rest a great deal. She had occasional feelings of faintness when on her feet, and the intermittent abdominal pain continued. Her discomfort ultimately became so great that she was admitted to the hospital on January 29 for complete bed rest. The pregnancy was then in its twenty-seventh week. It was noted that she was dyspneic and tired; there was mild ankle edema, no hypertension. Four fetal hearts could be heard on auscultating over the four quadrants of the abdomen. From then on she was continuously confined to bed until she went into labor on March 29, 1944, which was thirty-five and one-half weeks from the time of her last menstrual period.

To the foregoing a few more details may be added. Her weight increased from 118 pounds before pregnancy to 154 pounds a week before delivery, a total increase of 36 pounds. Her blood pressure was low throughout, varying from 96/70 to 130/80 just before delivery. On most days it was 110 to 116 systolic and 70 to 80 diastolic. The urine was albumin-free throughout. There was no general edema although there was slight puffiness of the ankles before she was confined to bed. Her abdominal girth, at the level of the umbilicus, was 46½ inches, a week prior to delivery. The red blood count continued good throughout. Four days prior to delivery it read: hemoglobin, 14 Gm. (97 per cent); red blood cells, 4,560,000.

For the last four weeks of the pregnancy our residents and nurses recorded the rates of the four fetal hearts, which could be easily distinguished from each other in the four quadrants of the abdomen. It is interesting to note that the rates varied considerably and did not show any constant ratio to each other.

Fetal Heart Rates at Various Intervals in Last Month of Pregnancy

138 130	129 195	140 138	126 142
148 128	136 132	122 166	130 138

Delivery Notes.—Multiple pregnancy, multiple birth; thirty-five and one-half weeks.

A: Vertex, L. O. A.

B: Frank breech, L. S. A.

C: Vertex, L. O. A.

D: Frank breech, R. S. A.

Mediolateral episiotomy with repair.

At intervals in the last month the uterus was irritable and she leaked fluid intermittently; this increased considerably during the last week of her pregnancy. On March 19 a large piece of tissue was passed per vaginam. Examination of this showed it to be degenerated decidua.

About 3 A.M. on March 29, thirty-five and one-half weeks after the last menstrual period, contractions at five-minute intervals were noted. The patient was observed over a period of five hours, during which time the contractions became more intermittent and irregular.

Rectal examination at 8 A.M. revealed the cervix to be almost fully dilated with only a small part of the anterior lip remaining; the vertex of Baby A was at the spines.



Fig. 1.—X-ray taken at four and one-half months (retouched).

She was taken to the delivery room, was given $\frac{1}{150}$ grain of scopolamine and 2 c.c. hykinone intramuscularly, and prepared for delivery. Vaginal examination confirmed the rectal examination of eight o'clock. At 10:30 A.M. the first sac was ruptured. Baby A presented by vertex, L. O. A. After short, very irregular contractions, over a period of twenty minutes, with bearing-down efforts on the part of the patient, the head descended to the pelvic floor, and following a right mediolateral episiotomy she spontaneously delivered a normal, lusty female infant. Time: 10:52 A.M.

Following delivery of Baby A, the tone of the uterus improved considerably. She was given a few whiffs of nitrous oxide and oxygen and the second sac was ruptured at 10:56 A.M.

Baby B presented as a frank breech, L. S. A. After several contractions the breech descended to the pelvic floor and delivery of a lusty male infant occurred at 11:03 A.M.

Examination then revealed Baby C presenting as a vertex. The third sac was ruptured at 11:13 A.M.

Uterine tone, momentarily, was poor and the cervix closed down to about three fingers' dilatation. Several good contractions followed, and Baby C delivered as a spontaneous L. O. A. at 11:18 A.M.

The fourth sac was ruptured at 11:21 A.M. and Baby D presented as a frank breech, R. S. A.

Uterine tone improved considerably. The breech descended to the pelvic floor and spontaneous delivery ensued of a normal, but somewhat smaller, female infant. This last baby cried rather feebly but improved rapidly. Time: 11:23 A.M.

A half cubic centimeter of pituitrin was administered following the birth of the last baby.



Fig. 2.—X-ray taken at seven and one-half months (retouched).

The uterus contracted down firmly; the placenta and membranes separated promptly and the third stage was concluded within seven minutes of the birth of last baby. Time: 11:30 A.M.

Estimated blood loss: 200 cubic centimeters.

Total duration of second and third stages of labor was one hour.

Another $\frac{1}{2}$ c.c. of pituitrin was administered intramuscularly and 1 c.c. of ergotrate intravenously. The tone of the uterus was excellent. An infusion was started and later the normal saline was replaced with blood. Blood pressure was 120/80 at the beginning of the second stage and 130/90 at the end of the labor. A sandbag was placed on the abdomen as a precaution against dilatation of the abdominal veins. The episiotomy wound

was repaired with No. 0 chromic catgut. The anesthetic used was nitrous oxide and oxygen, which was given intermittently in small amounts as occasion demanded.

Placenta and Membranes.—The placental mass was rectangular in shape and evidently formed by the fusion of four separate units between which are definite clefts, which show on the maternal surface (Fig. 3). The color is uniformly dark brownish red. There is a notable absence of infarcts. On the fetal surface each cord is attached eccentrically within its individual amniotic sac. The cord vessels do not pass across the partitions. (Fig. 4.)

The whole placenta measured 37 cm. in length, 23 cm. in width, and 3 cm. in thickness. It weighed 1,900 grams. Size: 15 by 9 by $1\frac{1}{4}$ inches. Weight: $4\frac{1}{2}$ pounds.

Microscopic examination of the placental tissue revealed nothing abnormal. Sections through the individual partitions between the sacs showed that each was made up of amniotic walls on each side with chorionic membrane between. The latter contained degenerated chorionic villi. (Fig. 5.)

All of these characters establish the case as one of quadriovular quadruplet pregnancy.



Fig. 3.—Maternal aspect of placenta. Note the definite clefts dividing it into four separate areas.

The Babies.—There were three females and one male. As already stated, examination of the placenta and membranes indicated that each was developed from a separate ovum. They are, therefore, quadriovular quadruplets. Dr. Harry J. Cohen, the pediatrician who has taken care of them since they left the hospital, reports that, at 7 months of age, they have no striking resemblances and can easily be distinguished from one another.

The preponderance of females is in conformity with the statistics of plural births. In the Statistical Bulletin of the Metropolitan Life Insurance Company of May, 1944, it is stated that "The ratio of females to males at birth appears to increase as the number of children born at one confinement increases. For single births there are 94 females born for every 100 males. For twins the figure rises to 97 per 100 males. In the higher order of plural births the sex ratio is reversed, and females are in the majority. For triplets there are 101 females born for every 100 males, and for quadruplets the ratio is as high as 156 to 100."



Fig. 4.—Maternal aspect of placenta. Four separate sacs with eccentric insertion of cords.

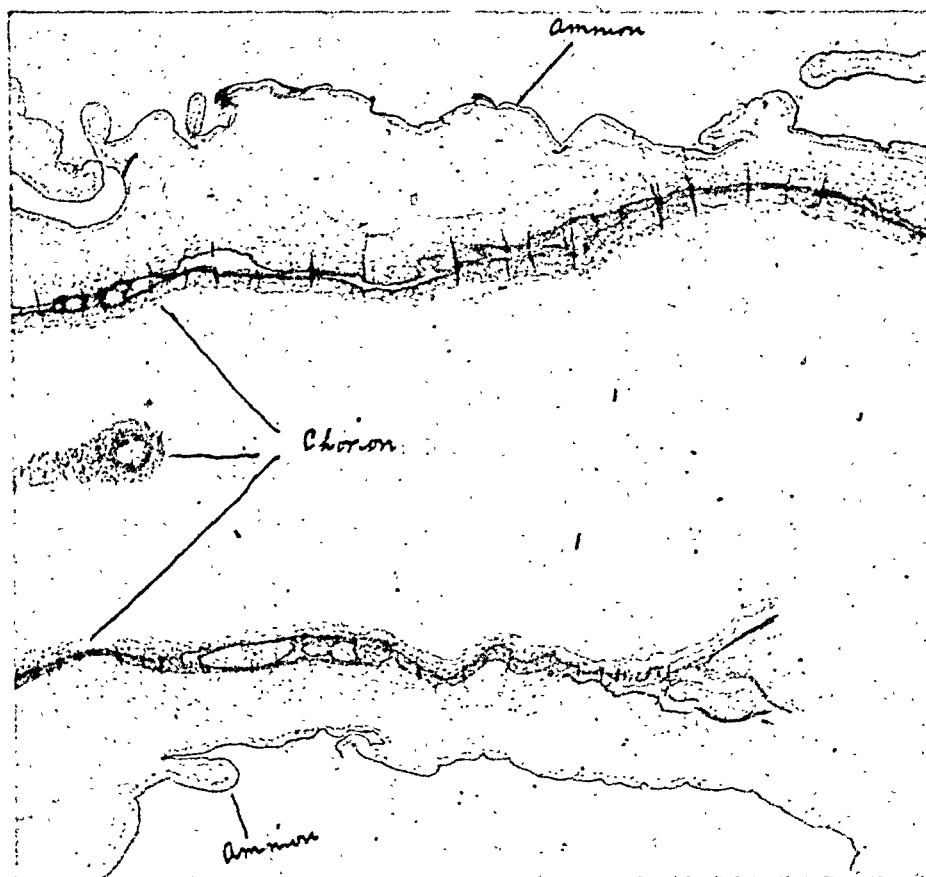


Fig. 5.—Cross section of the membranes between two of the amniotic cavities. Note the amniotic lining to each sac with the layer of chorion with degenerated villi covering it. The two chorionic surfaces are separated artificially in the preparation of the specimen.

The weights of the babies at birth were as follows:

- Baby A, female, 2,270 grams (5 pounds)
- Baby B, male, 2,270 grams (5 pounds)
- Baby C, female, 2,160 grams (4 pounds, 12 ounces)
- Baby D, female, 2,200 grams (4 pounds, 13 ounces)

After small initial losses, all of them had regained their birth weight by the eighth day, and thereafter they continued to gain so that on discharge from the hospital on the forty-eighth day they weighed, respectively: 8 pounds; 7 pounds, 11 ounces; 8 pounds, 4 ounces; and 7 pounds, 6 ounces.

At 7 months they weighed: 17 pounds, 13 ounces; 16 pounds, 1 ounce; 17 pounds, 1 ounce; and 16 pounds, 4 ounces.

All the babies were perfectly developed except Baby C who had a defect of the right ear with atresia of the external auditory canal. I am informed that a paternal aunt has a similar congenital anomaly.

All showed a fall in hemoglobin and red blood cell count following birth, and all had a moderate degree of anemia at the time of discharge from hospital. The hemoglobin percentages then were, respectively: 63 per cent, 54 per cent, 62 per cent, and 66 per cent. The red cell counts were: 2,240,000; 2,200,000; 2,400,000; and 2,540,000.

The babies were kept in incubators for a few days and then in ordinary cribs in the premature nursery. None were breast fed. All were on the usual formula for children of their weight. All were given iron in the form of ferrous sulfate.

At seven months the hemoglobin of each was 75 per cent. The children had developed normally both physically and mentally. The boy and one of the girls each had two teeth. The boy was the most active and energetic of the group. He could crawl on hands and knees the length of the crib.

Dr. Philip Levine was greatly interested in determining the blood types of the members of the family. He reported them as follows:

	<i>Group</i>	<i>Anti-Rh</i>	<i>Anti-Rh₁</i>	<i>Hr</i>
Father	OM	Pos.	Pos.	Neg.
Mother	OMN	Pos.	Neg.	Pos.
Baby A	OMN	Pos.	Pos.	Pos.
Baby B	OM	Pos.	Pos.	Pos.
Baby C	OM	Pos.	Pos.	Pos.
Baby D	OM	Pos.	Pos.	Pos.

The father is homozygous for the Rh factor because he is negative for Hr. Accordingly, his genotype is Rh₁Rh₁. The mother is Rh₂ and this type behaves genetically like a homozygous Hr. All offsprings must therefore be heterozygous for the Rh factors, i.e., Rh₁Rh₁, and this is exactly what is shown by the results.

Comments

The successful outcome of this case, I believe, is due to the bed rest and quiet this patient had in the last two months of her pregnancy. There was uterine irritability all through this time and toward the end there was leaking of fluid like liquor amnii and even the expulsion of a piece of degenerated decidua. Under these circumstances I believe labor would have set in much sooner had she not been kept at rest. Whether the fluid was really liquor amnii or not, I cannot be certain, but we do know that each amniotic sac was apparently intact at the time of labor. The origin of the fluid may, therefore, have been extraovular, so-called hydrorrhea gravidarum.

The ease of the labor is noteworthy. Uterine tone was fairly good throughout, increasing as each successive baby was born. All of the amniotic sacs were ruptured artificially as soon as the uterus contracted down following the delivery of the preceding child. The episiotomy minimized fetal trauma. In spite of the size of the placenta it separated and was expelled promptly and there was a minimal loss of blood.

There was no postpartum shock or fall of blood pressure following the delivery, in fact the blood pressure was higher at the end of labor than it had ever been during the pregnancy.

The puerperium was uneventful. Uterine involution was slower than average, the fundus being still palpable above the pelvic brim at the end of the second week. At the end of two months the uterus was of average size and in good position. The tone of the abdominal muscles has never been fully restored.

A PERITONEAL STAINING TECHNIQUE FOR EXTRAPERITONEAL CESAREAN SECTION

MAJOR GEORGE A. BOURGEOIS, M.C., ARMY OF THE UNITED STATES

(From the Section of Obstetrics and Gynecology, Surgical Service, AAF Regional Station Hospital, Mitchel, Field, N. Y.)

EXTRAPERITONEAL cesarean section is steadily gaining acceptance as the procedure of choice for abdominal delivery of potentially or actually infected parturients with obstructed labor.¹⁻²⁰ In spite of recent improvements in technique the operation remains difficult, and experienced operators may encounter trouble in performing it.

The commonest technical error, inadvertent puncture of the peritoneum, is corrected by ligature or suture. Subsequent dissection of the peritoneofascial flap is then complicated by a weak area liable to secondary rupture. Repair of the rent decreases the size of the flap, requiring compensatory dissection to provide room for delivery of the infant.

A peritoneal staining technique was conceived of to facilitate dissection of the peritoneofascial flap, and to aid in preventing injury to it. To accomplish this the flap is stained before its dissection by introducing dye into the peritoneal cavity. The stained peritoneum provides, in contrast to the unstained hernia-like sac sometimes difficult to locate or easily lost, a landmark to guide dissection of the peritoneofascial flap from the bladder.

Properties considered in selecting a dye for this purpose were (1) low general toxicity, (2) absence of untoward peritoneal reaction, (3) staining ability, and (4) availability. Phenolsulfonphthalein and methylene blue were chosen for experiment. The staining reaction of phenolsulfonphthalein was weak in the first clinical trial, and in subsequent operations methylene blue was found to be more satisfactory.

Peritoneal Staining Technique

After preparation of the vagina and sterile vaginal examination, the urinary bladder is emptied by catheter and refilled with about 250 c.c. of 0.001 per cent phenolsulfonphthalein solution.* The catheter is left in the bladder. A midline incision is made down to the transversalis fascia which is stripped by blunt dissection from the undersurface of the recti muscles. A small opening is then made into the peritoneal cavity at the extreme upper pole of the incision. Through this opening a soft rubber catheter, to which a syringe containing 5 c.c. of 0.5 per cent aqueous methylene blue solution has been attached, is inserted into the peritoneal cavity toward the bladder. Any free peritoneal fluid is aspirated. The bladder is then emptied and the dye injected over its peritoneal surface. Injection is performed slowly with simultaneous manipulation of the catheter tip through the transversalis fascia and peritoneum to bring the dye in contact with all of the future peritoneofascial flap. During this procedure the edges of the peritoneal opening are elevated by an assistant to prevent overflow of dye onto extraperitoneal tissues. When injection is completed the catheter is withdrawn. The peritoneum is then closed transversely with a continuous suture of fine chromic gut and the transversalis fascia longitudinally with a continuous suture of the same material. Occasionally the tissues involved will accept only one layer of suture. The resulting sharply demarcated blue peritoneum guides subsequent dissection of the peritoneal flap.

*The 0.001 per cent phenolsulfonphthalein solution is prepared by adding to 250 c.c. of sterile distilled water 24 mg. of phenolsulfonphthalein and 30 Gm. of sodium bicarbonate. Both solutions are sterilized by autoclaving.

Report of Cases

This technique has been employed in ten extraperitoneal cesarean sections. In general the indications for extraperitoneal section set forth by Cosgrove and Norton⁴ have been followed. These are (1) previous vaginal examination or attempts at delivery, (2) clinical evidence of infection, (3) duration of labor in excess of twenty-four hours or (4) duration of membrane rupture in excess of eight to twelve hours. In Cases 3 and 7 the extraperitoneal route was employed electively to augment experience with the staining technique.

CASE 1.—A 26-year-old primigravida, 5 feet tall and weighing 171 pounds, was first seen on March 22, 1943. Since she was only four weeks from term, no pelvic examination was done. Overriding of the fetal head was noted two weeks later. When the patient entered the hospital in early labor, roentgenologic examination disclosed a small gynecoid pelvis with evidence of cephalopelvic disproportion. After 19 hours of strong labor and 12 hours of membrane rupture, her temperature rose to 101.6° F. The cervix was 7 cm. dilated and the head gave no promise of engagement. On April 28, 1943, an 8-pound, 6-ounce male infant was delivered by extraperitoneal cesarean section. The patient experienced one day of morbidity,* her highest temperature being 102° F. Both mother and infant left the hospital in good condition on the sixteenth postoperative day.

CASE 2.—A 21-year-old primigravida, 4 feet 10 inches tall, was first seen at thirty-five weeks' gestation. No pelvic examination was performed, but a note was made that roentgenologic examination of the pelvis should be made if the head was unengaged at the onset of labor. Such examination revealed a small gynecoid-android pelvis with much molding of the unengaged head. With unsatisfactory progress during 27 hours of labor and 9 hours of membrane rupture, extraperitoneal cesarean section was performed on May 5, 1943, with delivery of a 7-pound, 2-ounce male infant. The patient experienced one morbid day, and was discharged from the hospital in good condition on the fifteenth postoperative day.

CASE 3.—A 35-year-old secundigravida, whose first pregnancy three years previously had terminated in spontaneous birth and neonatal death because of cerebral hemorrhage of a 6-pound 9-ounce infant, entered the hospital in early labor. Clinically her diagonal conjugate had measured 9.5 cm., and x-ray had disclosed a platypelloid pelvis. After 10 hours of moderate labor without promise of engagement of the overriding head, pregnancy was terminated on May 22, 1943, by cesarean section, by election of the extraperitoneal type. The infant weighed 6 pounds, 10 ounces. The patient experienced no morbidity; both she and her infant left the hospital in good condition on the twelfth postoperative day.

CASE 4.—A 35-year-old primigravida was noted during her prenatal course to have a small gynecoid pelvis. Going into labor at thirty-nine weeks' gestation with a frank breech presentation, she made satisfactory progress until the cervix was completely dilated, after which the breech failed to advance during a nine-hour period. After 16 hours of labor with an equal period of membrane rupture, extraperitoneal cesarean section was performed on July 14, 1943, with delivery of a 6-pound 2-ounce female infant. The patient experienced two morbid days, her highest temperature being 101° F. Both she and her infant were discharged from the hospital in good condition on the eighteenth postoperative day.

CASE 5.—A 25-year-old primigravida, 4 feet 10 inches tall, with a small gynecoid pelvis by both clinical and x-ray examination, failed to engage the head after 27 hours of labor and eight hours of membrane rupture. An 8-pound 12-ounce male infant was delivered by extraperitoneal cesarean section on Aug. 14, 1943. The patient experienced two morbid days, her highest temperature being 101.2° F. She and her infant were discharged in good condition on the thirteenth postoperative day.

CASE 6.—A 33-year-old primigravida with an apparently adequate gynecoid pelvis by both clinical and roentgenologic examination went into labor at term. A better than average-sized fetus presented in right occipitoposterior. After 46 hours of labor and 25 hours of membrane rupture, the cervix, although well effaced, was only 3 cm. dilated, and the liquor amnii had become foul. The lower uterine segment was tender, and so thin that the infant's

*Morbidity Standard: Temperature 100.4° F. or above on any day excluding the first twenty-four hours after delivery.



Plate I.—The stained peritoneofascial flap is elevated from the lower uterine segment. The bladder appears at the inferior angle of the incision. (Engraving from Official Photograph, U. S. Army Air Corps, Base Photo Section, Mitchel Field, N. Y.)

chin and anterior arm could be easily palpated through the abdominal wall. A 9-pound 6-ounce male infant was delivered by extraperitoneal cesarean section on Oct. 3, 1943. During its dissection the peritoneofascial flap was inadvertently torn by traction. A velvety smooth blue peritoneal surface presented through the rent. There was no detectable free fluid and no escape of methylene blue onto the extraperitoneal tissues. The tear was immediately repaired. The patient experienced four morbid days, her highest temperature being 102.4° F., and she was discharged with her infant in good condition on the seventeenth postoperative day.

CASE 7.—A 26-year-old primigravida, 4 feet 10 inches tall, presented a small platypeloid pelvis with diagonal conjugate of 9 cm. on antepartum pelvic examination. After 17 hours of moderate labor during which the head persistently overrode the symphysis, an 8-pound 6-ounce male infant was delivered on Oct. 30, 1943, by the abdominal route, by election of extraperitoneal type. The patient experienced two morbid days, her highest temperature being 102.4° F. She was discharged from the hospital with her baby on the thirteenth postoperative day.

CASE 8.—A 21-year-old primigravida with a gynecoid-android pelvis went into labor at forty-five weeks' gestation by date. After 80 hours of labor, of which 56 hours were considered effectual, and after 33 hours of membrane rupture, the liquor amnii was becoming foul. The cervix was 4 cm. dilated. A 7-pound 11-ounce male infant was delivered on Nov. 29, 1943, by extraperitoneal cesarean section using 2.5 c.c. of methylene blue solution. The peritoneofascial flap was incompletely stained, and accidentally punctured in an unstained area. The puncture was immediately repaired. The patient experienced two morbid days, her highest temperature being 103.8° F., and was discharged in good condition, together with her infant, on the thirteenth postoperative day.

CASE 9.—A 23-year-old primigravida at term presented an unengaged head after 38 hours of labor and an equal duration of membrane rupture. The cervix had remained 6 cm. dilated for eight hours. A 7-pound 4-ounce female infant was delivered by extraperitoneal cesarean section on April 21, 1944. Because the methylene blue solution was injected in the presence of a distended bladder, the peritoneofascial flap was incompletely stained. The flap was accidentally punctured, and immediately repaired. The patient experienced four morbid days, her highest temperature being 103.2° F., and was discharged together with her infant on the nineteenth postoperative day.

CASE 10.—A 28-year-old primigravida at thirty-nine weeks' gestation entered the hospital in early labor with a frank breech presentation. The membranes had ruptured two hours after the onset of labor. The cervix was completely dilated and the breech in midpelvis after nine hours of labor. Because no further descent of the breech occurred during the next five hours, sterile vaginal examination was performed. It revealed firm soft tissues and a gynecoid pelvis which seemed adequate except for a contracted outlet. Roentgenologic examination confirmed the latter. During eight hours subsequent labor, the uterine contractions became weaker and less frequent, and no further advance of the presenting part occurred. It was explained to the patient, whose husband was overseas, and to her mother that choice of management lay between breech extraction and cesarean section. The maternal and fetal hazards of each were stated. They chose abdominal delivery. After 22 hours of labor and 20 hours of membrane rupture, an extraperitoneal cesarean section was performed on July 17, 1944. The infant, whose weight had been judged average prior to delivery, weighed 4 pounds, 14 ounces. The patient experienced two morbid postoperative days, her highest temperature being 101.4° F. She left the hospital together with her infant in good condition on the fifteenth postoperative day.

Case 4 was the first extraperitoneal cesarean performed by one member of the surgical staff; it was accomplished with facility. Cases 1, 2, 3, 5, 7, 8, 9, and 10 were performed by the writer. There were no bladder or ureteral injuries. Postoperative abdominal distention was minimal, nausea was rare, and there was no postoperative vomiting in any case. In no instance did evidence of peritoneal irritation develop. The urine of all patients was free of methylene blue within forty-eight and usually within thirty-six hours of operation. Postoperative morbidity averaged two days. The postoperative hospital stay averaged fifteen days. There was neither maternal nor fetal mortality. Six-week and subsequent postpartum examinations have shown that all ten patients possess well-involuting and freely movable uteri.

Technical Considerations

The dark blue edge of the stained peritoneofascial flap serves as a reliable guide for dissecting it from the bladder and uterus. There is clear delineation of the inferior margin of the parietovesical peritoneal fold. The latter varies from patient to patient in contour, symmetry or lack of it, and level of bladder attachment. The initial incision through the transversalis and anterior perivesical fasciae is made transversely about $\frac{1}{2}$ inch below the stained fold. The perivesical fascia is then bluntly dissected from the bladder muscularis laterally to the point of junction of the bladder, uterus, and stained uterovesical fold of peritoneum. The latter constitutes a landmark for accurate incision through the posterior perivesical and anterior periuterine fascial layers, exposing the anterolateral aspect of the lower uterine segment. Dissection to the same degree is repeated on the opposite side of the bladder. The two anterolateral areas of lower uterine segment thus exposed are then made continuous by blunt dissection with the finger of the entire uterovesical fold from the lower uterine segment. This frees the bladder circumferentially so that it is attached to the peritoneofascial flap only on its superior surface. Gentle traction on these structures then permits their complete separation by sharp and blunt dissection. As others have noted, division of the peritoneofascial flap from the bladder in the urachal area usually requires sharp dissection.

Strands of tissue stained by methylene blue may be found in the more adherent urachal area, and occasionally in the superolateral areas of the exposed lower uterine segment. Such areas present a variegated appearance, however, and are presumably the result of absorption of methylene blue into lymphatic channels draining the peritoneum. There is still good contrast between the bladder or uterus and the stained peritoneofascial flap, and in no instance has anatomical confusion arisen because of these areas.

In three cases the peritoneal cavity was inadvertently entered. In Case 6 the posterior fold of the peritoneofascial flap was accidentally torn by undue traction twenty minutes after injection of the dye. The solution had been completely absorbed. In Case 8 where an attempt was made to reduce the quantity of methylene blue solution to 2.5 c.c., there was incomplete staining of the peritoneofascial flap and it was accidentally opened in the unstained area. In Case 9 the methylene blue solution was injected into the peritoneal cavity in the presence of a distended bladder. This resulted first in slight overflow of the solution at the site of injection, and second in incomplete staining of the peritoneofascial flap with its subsequent violation. These experiences emphasize the importance of injecting an adequate amount of dye solution in the presence of an empty bladder.

Discussion

Criticism may be directed at intentional opening of the peritoneal cavity in an operation whose primary purpose is elimination of peritonitis. However, the peritoneal incision is placed where both tension on the peritoneofascial flap and likelihood of tearing it during subsequent dissection are minimal. As an added precaution the incision is closed, when possible, in two staggered layers. Regardless of the manner of closure, no leakage of dye through the peritoneal incision has occurred in any of the operations performed; it follows that bacteria are unlikely to penetrate in the reverse direction.

There is a possibility that accidental rupture of the peritoneofascial flap will permit the escape of dye onto the extraperitoneal tissues thus creating anatomical confusion. In the one instance where the stained flap was torn by undue traction twenty minutes after injection of the dye, no dye escaped. It had been absorbed within that time. Only further experience can answer the questions of how long such absorption requires, and what the result of rupture before absorption of the dye may be.

Contrary to what one might expect, handling of the stained peritoneofascial flap does not result in staining of gloves, instruments, or the operative field.

Objection may be made to calling a section performed by the peritoneal staining technique extraperitoneal. Since most reported series of extraperitoneal cesarean sections include operations where the peritoneal cavity has been

violated, and since the purpose of extraperitoneal operation in regard to the patient's welfare is accomplished in spite of such violations, there is some argument for classifying the peritoneal staining technique with other extraperitoneal operations. It is suggested that techniques where the peritoneum is deliberately opened and then closed, such as that of Aldridge¹ and the one described here, might be termed pseudoextraperitoneal. This would distinguish such operations from both the true extraperitoneal operations and those performed by peritoneal exclusion.

Summary

A peritoneal staining technique to facilitate recognition of the peritoneofascial flap and aid in preventing its accidental puncture is presented. A single small premeditated opening is made into the peritoneal cavity to permit injection of dye substance in the area of the future peritoneofascial flap. Five cubic centimeters of 0.5 per cent aqueous methylene blue solution, introduced through the peritoneal opening by catheter, has been found satisfactory for this purpose. It is important that the bladder be empty during injection of the dye. The peritoneal incision is closed before dissection of the flap is begun. Demarcation of the peritoneum by color provides a reliable guide for dissection of the peritoneofascial flap.

Ten extraperitoneal cesarean sections have been performed in this manner without maternal or fetal mortality. The peritoneal cavity was accidentally entered three times, once because of undue traction on the peritoneofascial flap, twice because the flap was incompletely stained. Incomplete staining of the peritoneofascial flap occurred in the first instance because the amount of dye was insufficient; in the second because injection of the dye was performed in the presence of a distended bladder. There was no injury to bladder or ureters. Convalescence of all patients was free of any peritoneal irritation or postoperative vomiting. All uteri were well involuted and freely movable at follow-up examinations.

Various considerations arising from use of the technique are discussed.

References

1. Aldridge, A. H.: *AM. J. OBST. & GYNEC.* 33: 388, 1937.
2. Briscoe, C. C.: *AM. J. OBST. & GYNEC.* 48: 16, 1944.
3. Burns, H. T.: *AM. J. OBST. & GYNEC.* 19: 759, 1930.
4. Cosgrove, S. A., and Norton, J. F.: *J. A. M. A.* 118: 201, 1942.
5. Cooke, W. R.: *AM. J. OBST. & GYNEC.* 35: 469, 1938.
6. Daichman, I., and Pomerance, W.: *AM. J. OBST. & GYNEC.* 47: 678, 1944.
7. Eisaman, J. R., and Austin, B. R.: *Pennsylvania M. J.* 45: 813, 1942.
8. Irwin, L. C.: *West. J. Surg.* 49: 158, 1941.
9. King, E. L.: *AM. J. OBST. & GYNEC.* 40: 860, 1940.
10. Manahan, C. P., Connally, H. F., Jr., and Eastmen, N. J.: *AM. J. OBST. & GYNEC.* 44: 999, 1943.
11. Marr, J. P.: *New York State J. Med.* 44: 1230, 1944.
12. Norton, J. F.: *AM. J. OBST. & GYNEC.* 40: 209, 1940.
13. Phaneuf, L. E.: *AM. J. OBST. & GYNEC.* 40: 603, 1940.
14. Idem: Discussion of article by Mohler, R. W.: *AM. J. OBST. & GYNEC.* 45: 466, 1943.
15. Pieri, R. J., and Irving, F. R.: *New York State J. Med.* 42: 25, 1942.
16. Ricci, J. V.: *AM. J. Surg.* 47: 33, 1940.
17. Steele, K. B.: *AM. J. OBST. & GYNEC.* 19: 747, 1930.
18. Waters, E. G.: *AM. J. OBST. & GYNEC.* 39: 423, 1940.
19. Idem: *West. J. Surg.* 50: 512, 1942.
20. Williamson, H. C., and Goldblatt, M. E.: *AM. J. OBST. & GYNEC.* 45: 103, 1943.

PRIMARY CARCINOMA OF THE FALLOPIAN TUBE

J. ERNEST AYRE, M.D., W. A. G. BAULD, M.D., AND P. J. KEARNS, M.D.

MONTREAL, QUEBEC

(From the Department of Obstetrics and Gynecology, Women's Pavilion, Royal Victoria Hospital, McGill University)

THE Fallopian tubes, by repute, are highly resistant to malignant disease. Primary tubal carcinoma is one of the most rare of gynecologic tumors. Less than four hundred cases have been reported in the literature to date. From a consecutive series of 30,000 gynecologic admissions to the Women's Pavilion of the Royal Victoria Hospital, only two cases were found. In 1925 it was remarked by S. J. Cameron¹ that this disease was so rare that many gynecologists had never encountered it. It fell to the lot of one of us (W. A. G. B.), to find both our cases at operation.

It occurs chiefly in the cancer age (40 to 60 years) although cases have been reported as early as the second decade and as late as the eighth. It is bilateral in about one-third of the cases. Multiple pelvic pathology has been found in association in most cases, e.g., chronic salpingitis, ovarian cystomata, uterine fibroids, etc.

Some authors have expressed the view that salpingitis was a precursor of the disease, predisposing to its onset. In opposition to this opinion, it may be reasoned that salpingitis is the commonest tubal disease while malignancy is the most rare. Therefore, there must be other more potent etiological factors concerned in its production. The associated inflammatory features in this case are most interesting as will be shown later.

According to Doran² the presence of the tumor itself may produce a chronic inflammatory reaction, which may close the tube and simulate a hydrosalpinx. This proves to be a defense mechanism slowing the spread via the tubal ostium. In addition, pressure within the closed sac produces pain which should cause the patient to seek medical advice at an earlier date. When the tube is open there may be no symptoms until the abdomen begins to enlarge because of ascites and peritoneal metastases.

In an effort to explain the relative infrequency of tubal as compared with endometrial cancer it is interesting to contrast the two epithelia. Both tissues arise from the Müllerian ducts. The uterine epithelium is extremely active and is constantly in a state of flux, blossoming forth so resplendent in response to the ovarian growth and secretory hormones, only to wilt and die quickly on the sudden withdrawal of its nourishing stimulus, at the termination of its short fruitless cycle. It undergoes tremendous hypertrophy during pregnancy and is exposed to much more injury and rapid transformation than is the tubal mucosa. In contrast, the tubal epithelium is quite inactive and is well protected. Although it reacts to the cyclic changes of menstruation, they are insignificant. There is no monthly desquamation to be followed by rapid regeneration, and even during pregnancy the tubal mucosa alters little. Therefore, it would seem that these conditions produce a situation which offers scant opportunity for cellular overgrowth, hyperplasia, or unusual cytologic activity.

When found in its early stages, the tumor may be represented merely by a firm nodular thickening resembling an olive or a sausage enclosed within an intact tubal wall. In some cases a hydrosalpinx or a hematosalpinx may be found proximal to the tumor. This association would tend to confuse the diagnosis grossly, suggesting a purely inflammatory condition.

In the advanced case the gross appearance is that of a large ovoid mass simulating a pyosalpinx except that the external surface is smooth and solid and free of adhesions. The tubal orifice may be open, in which case papillary projections frequently grow out, spreading along the peritoneum, pelvic and abdominal organs by direct extension.

When the tube is sectioned transversely, the center is filled with a thickened papillary mass which is friable, hemorrhagic, and necrotic in some areas, growing on a fibrous groundwork with connective tissue septa running throughout. The tubal wall may be of normal thickness or it may be very thin over the mass due to stretching.

Two microscopic types were originally described by Sanger and Barth, the papillary and the papillary alveolar. Most cases have been placed in the first group, the papillary tendency being the predominant characteristic, while those cases exhibiting a glandular pattern have been relegated to the latter group. Some of the more recent authors are in agreement with Liang⁴ who, in 1926, following a careful pathologic study of the subject, arrived at the conclusion that there was only one type, the alveolar morphologic arrangement representing merely a different stage of the process.

Wharton and Krock⁶ state that their series of 14 cases showed an identical histological pattern, with only minor variations in growth and morphology. They state that although it may be true that some tumors are largely alveolar and others papillary, there is at present no evidence that they are inherently distinct or that their behaviour is different in regard to malignancy, methods of extension, or clinical characteristics.

The neoplasm has its origin in the tubal mucous membrane. There is a tendency at first glance to label the lesion as an adenocarcinoma of the tube. But this is incorrect as there are no glands in the tube. Abnormal growth merely produces a pseudoglandular picture. Various stages of metaplasia may be observed in any one case. In some areas small papillary growths replace the fine wavy tufts of normal mucosa. In these papillae there is little connective tissue framework, the growth consisting chiefly of single layers of tubal epithelium, arranged in glandlike pattern, suggesting the picture found in adenocarcinoma of the endometrium. The epithelial cells themselves may show no abnormal change but the pattern shows malignant disease. Our case, however, shows malignant cytology as well as morphology.

In other papillae in which the process is further advanced, there is a heaping up of epithelium so that it may be several layers thick or may even form solid nests of cells. The cells become more and more irregular in shape and atypical and the nuclei become hyperchromatic.

Large overgrown plicae appear to grow centrally from a notably intact wall. The tubal wall is usually free from invasion. As the papillae enlarge and press against each other, they unite to form solid masses of tissue. The alveoli are filled with hyaline secretion and the papillae tend to lose their individuality.

Mitotic figures, lymphocytic infiltration, and occasional areas of necrosis appear. This stage corresponds to the so-called papillary-alveolar type.

It should be noted in passing that extensive tubal tuberculosis may produce an adenomatous structure strikingly similar to that of malignancy, and careful study is necessary to permit an accurate differentiation.

Case Report

The patient was 51 years of age, born in Canada of Aryan stock, admitted to the Women's Pavilion of the Royal Victoria Hospital on Oct. 10, 1942. She complained of pain of an intermittent character in the left lower quadrant, first noticed twelve months ago. The pain radiated through to the back and occasionally down the left leg. For the past six months the severity of attacks had been exaggerated and one month ago bleeding from hemorrhoids had been noticed for the first time. Menstrual history unaltered. Cycle: 12 by 28 by 3. No menometrorrhagia, leucorrhea, or dysmenorrhea. Attacks of pain more frequent postmenstrually. Patient had been married nineteen years and had never been pregnant. Of interest in her past history was the fact that twelve years ago she underwent an operation to overcome sterility. The patient had been married seven years at this time without becoming pregnant. Postoperatively she developed pelvic cellulitis and phlebitis necessitating hospitalization for three months. Subsequently, a complete recovery was made and she had enjoyed good health up to the onset of the present trouble.

The family history was negative for cancer.

On examination a firm mass was felt in the pelvis on the left side and a laparotomy was performed.

At operation a mass the size of a baseball was found in the left tube extending into the broad ligament, its surface appearing smooth, convoluted, and congested. The fimbriated end of the tube was closed. On the opposite side a smaller tumor the size of an egg was found in the right tube. Both ovaries exhibited a normal appearance showing no involvement with the tumor growth. A panhysterectomy was performed.

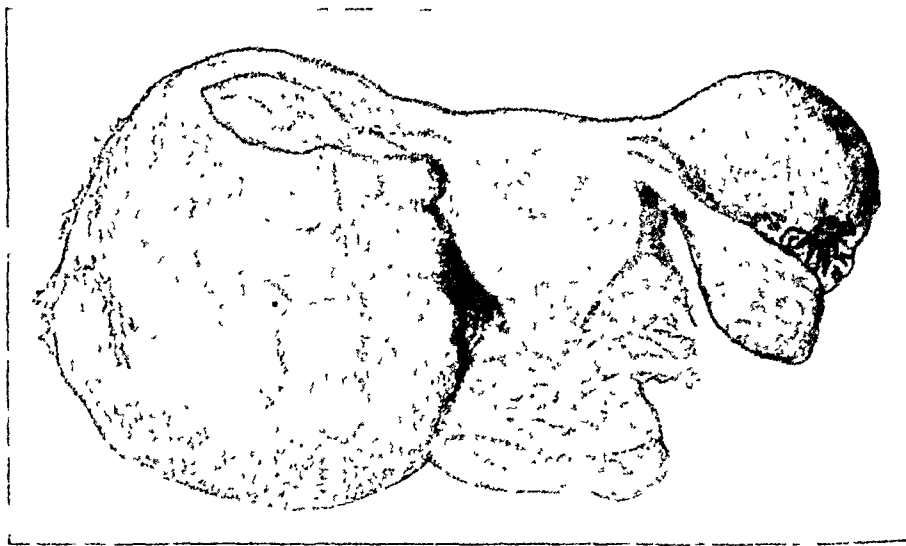


Fig. 1.—Gross appearance of pelvic organs following removal. Note the large tumor mass on the left side completely enclosed in enormously stretched tubal wall. The smaller tumor on the right presented a more smooth and firm consistency.

Gross examination of the removed organs revealed a normal-sized uterus measuring 8 by 6 by 4 cm. removed with cervix attached (Fig. 1). One or two marble-sized fibroids appeared on the posterior surface of the uterus. The endometrium appeared smooth and showed no gross lesion. The left adnexa exhibited a soft spherical tumor measuring 12 cm. in diameter, the surface of which consisted of the stretched tubal wall. The fimbriated end of the tube was closely bound to the tumor mass and the tubal ostium was closed. The left ovary appeared small and discrete. The right tube contained a small tumor located in the middle third of the tube, the mass appearing ovoid in shape measuring 6 by 4 cm. The right ovary was of normal size and was entirely free of adhesions and induration. When the tubal wall covering the larger tumor mass was incised, the tissue appeared soft and edematous, somewhat resembling decidual tissue. The tissue cut with a puttylike consistency and the outer part appeared quite homogeneous and numerous small spaces were opened up,

suggesting a glandular character. Towards the center of the mass, the fibrous stroma presented an arborescent appearance some parts of which were quite dense and exhibited a yellowish coloration resembling that of a corpus luteum. The smaller tumor exhibited similar characteristics except that its consistency was more firm and rubbery and its structure was homogeneous throughout.

Microscopic study of the tubal masses showed a mixed picture, the predominant characteristic being a formation of many huge hypertrophic plicae covered by extremely hyperplastic immature-appearing tubal epithelium with numerous papillary projections and dense adenomatous formations. (Fig. 3.) The epithelial tissue consisted of tall columnar



Fig. 2.—Honeycomb appearance with extensive agglutination of plicae simulating chronic follicular salpingitis.

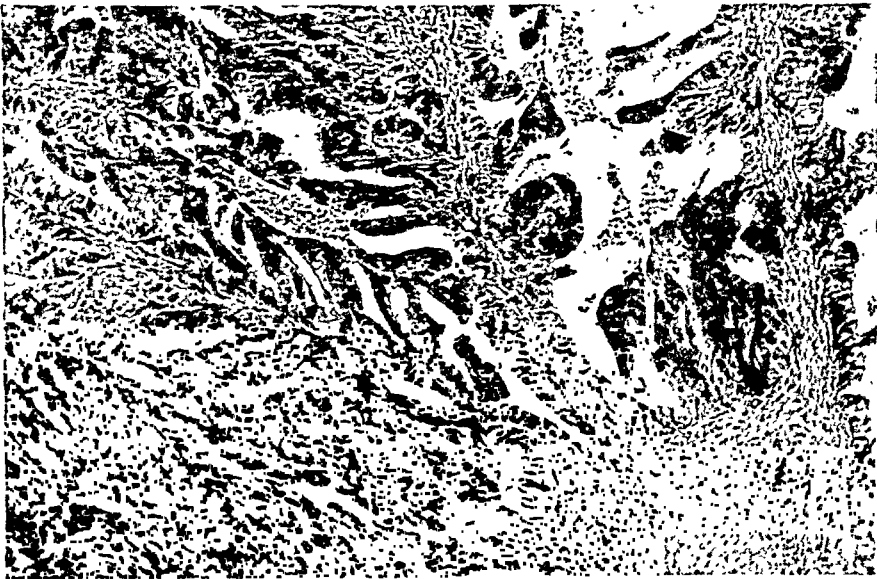


Fig. 3.—High-power study of plicae reveals malignant character of covering epithelium.

cells which in many areas appeared closely packed, tending to produce a solid structure in which there is noted pleomorphism and polychromasia, many of the nuclei appearing large and clear-staining with pyknotic nucleoli and numerous mitoses. Sections of the smaller tumor exhibited a uniformly solid sarcomatoid appearance (Fig. 4), with a pseudoglandular structure. Serial sections of the left tube taken from the cornual end distally toward the tumor show an interesting picture. In the cornual region the lumen is small with a few

stellate plicae covered by an epithelium exhibiting a hyperplastic tendency with some vacuolation. Another section of the tube more distally shows an extensive agglutination of the plicae producing a uniform honeycomb appearance throughout the lumen. The epithelium in this section appears quite benign, and the general appearance simulates an extensive follicular salpingitis (Fig. 2). Closer to the tumor the structure exhibits a more solid follicular appearance, while at the same time, the epithelium becomes more hyperplastic, assuming a more malignant structure (Fig. 3). Sections through the tumor proper present a variable appearance. Some show hyperplastic, but benign epithelium, while the morphologic structure is that of malignancy. Other sections present a definite picture of malignancy (Fig. 3) with invasion of the wall in some areas, although no area showed a complete breakthrough onto the surface.

The smaller tumor exhibited a different picture, in some areas the papillae appearing close-packed, producing a solid, almost sarcomatous appearance.

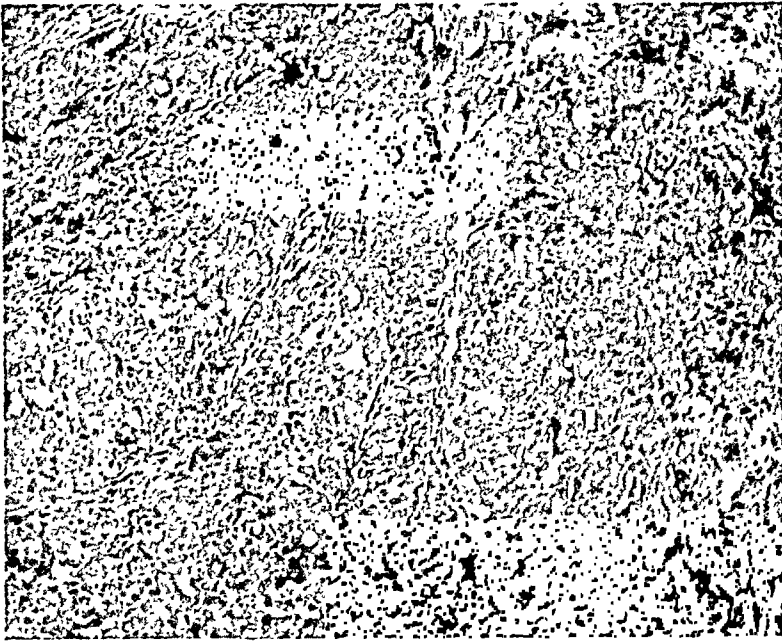


Fig. 4.—Solid arrangement found in smaller tumor presenting sarcomatoid appearance.

Discussion

Tubal carcinoma is a highly malignant lesion and very few cases are on record of a five-year cure. Spread occurs by lymphatic extension to the uterus and ovaries because of their proximity. In the first case reported from this Clinic in 1932, Kearns³ claimed that "metastasis occurred by invasion of the subepithelial structures of the mesosalpinx spreading by way of the lymphatics to the lumbar glands." Direct spread through the ostium of the Fallopian tube, implanting on pelvic and abdominal organs, seems to be quite frequent. This spread by "spill" often occurs early in the disease, leading to rapid dissemination and death.

Rarely are implants observed in the endometrium although fluid is believed to pass down from the tube and out via the vagina.

A striking difference between primary and secondary tubal cancer is the fact that primary almost never invades the tubal wall, whereas secondary growths almost always invade the tube from without.

The disease is seldom diagnosed clinically and infrequently is it made on the operating table. Usually the true nature of the lesion is only revealed by microscopic examination. This is unfortunate. The delayed diagnosis has added greatly to the mortality rate. Wharton and Krock estimate that fully two-thirds of the reported cases have had incomplete operations, a unilateral

salpingectomy being performed for supposed hydrosalpinx. Possibly the mortality figures would appear more favorable if the mass were sectioned at the time of the operation, the tentative diagnosis made, and a panhysterectomy performed.

Pain is the most characteristic symptom, produced by the stretching of the tubal wall. An abnormal vaginal discharge is almost always associated. This is usually profuse and of a purulent, watery or sanguineous character. Some authors have reported a symptom complex, in which severe lancinating pains are suddenly relieved by the release of a profuse watery discharge per vaginam. They express the opinion that the tubal tension of the accumulating fluid is relieved by the fluid forcing its way through the cornua and discharging from the uterus and vagina.

Menstrual disorders, backache, bladder symptoms, fever, gastrointestinal disorders, abdominal ascites, and cachexia may develop as the disease spreads. The pain is frequently sharp and colicky and may be accompanied by nausea and emesis. It tends to occur from month to month, increasing in severity as the disease progresses.

The mortality from primary carcinoma of the tube is extremely high. In 1926, Wechsler⁵ found only six three-year cures in 200 cases. The prognosis in this form of cancer should be better because pain is the first and most characteristic symptom, and this is what usually sends the patient to the doctor. Further, the tubal wall is seldom invaded, and, in those cases where the tubal ostium remains closed off, direct spread should not be rapid. In this case, symptoms of pain were noted for almost a year prior to operation at which time there was no gross evidence of spread. The extremely pessimistic statistics certainly paint a hopeless picture. Possibly, lymphatic metastasis occurs quite early. It must be borne in mind, however, that the figures presented are misleading. As we have stated above, fully two-thirds of these had incomplete operations. In addition, operation would tend to be delayed if the accompanying inflammation was diagnosed. Radiotherapy has been tried but with poor results, presumably for the same reasons that this form of therapy has proved disappointing in ovarian carcinoma.

This case of primary bilateral carcinoma of the tube presents several points of interest. The tissues appear generally quite clearcut and free from extensive necrotic degeneration which might otherwise destroy the cytology. While certain sections present a papillary appearance, others present a pseudoglandular or alveolar appearance. The second smaller tumor presents a definitely solid structure and so might be termed a solid carcinoma of the tube. This demonstrates that these are not three independent types of tubal carcinoma: the papillary, the alveolar, and the solid; but merely local variations in morphology.

The gradation of hyperplasia as shown in the serial sections, from the normal through the inflammatory stage to the malignant, is interesting. In view of the past history of tubal inflammation and sterility, one wonders how much of the follicular salpingitis (Fig. 2) may be a result of this, and how much may be the result of the presence of the malignancy. The theory that inflammation predisposes to malignancy would seem to be largely discounted as a major factor in as much as salpingitis is so common, and tubal carcinoma so rare. It would seem more logical that some inflammatory reaction would develop due to the presence of a tumor mass in the tube.

With such a formidable array of mortality statistics the prognosis would naturally be guarded in any case of carcinoma of the tube.

References

1. Cameron, S. J.: Brit. M. J. 2: 285, 1925.
2. Doran, Alban: J. Obst. & Gynaec. Brit. Emp. 6: 285, 1904.
3. Kearns, P. J.: Canad. M. A. J. 26: 73, 1932.
4. Liang, Z.: Virchows Arch. f. Path. Anat. 259: 577, 1926.
5. Wechsler, H. F.: Arch. Path. 2: 16, 1926.
6. Wharton, L. A., and Kroek, F. H.: Arch. Surg. 19: 849, 1929.
7. Mullins, D. F., and Mosteller, R.: AM. J. OBST. & GYNEC. 45: 1042, 1943.

1414 DRUMMOND STREET.

RELATIONSHIP OF MATERNAL WEIGHT GAIN AND WEIGHT OF NEWBORN INFANT*

JACOB S. BEILLY, M.D., F.A.C.S., AND IRVING I. KURLAND, M.D.,
BROOKLYN, N. Y.

(From the Department of Obstetrics and Gynecology, Beth-El Hospital)

MODERN obstetric practice with its emphasis on regular antepartum care and examination has materially contributed to the elimination of many possible complications of pregnancy and labor. There still remains, despite all this, the danger of encountering the large baby in labor. This problem has gained the attention of many, and numerous contributions have been made concerning the weight changes during pregnancy and the relation of mothers' gains to the weight of the newborn infants. Studies in the past have attempted to give some basis of anticipating the probable size of the fetus. Davis,¹ Slemons and Fagan,² Bingham,³ and Hanley⁴ have indicated that the weight of babies at term parallel the gains of mothers. McIlroy and Rodway⁵ reported that the weight of the infant was not directly dependent upon the increase in weight of the mother. Cummings⁶ believes that heredity plays the most important part in determining the size of the newborn infant, although the state of health of the mother would influence it to some extent. Toombs⁷ concluded that "the size of the child at the time of delivery is determined by factors quite distinct from this consideration, and in most instances, entirely beyond our control."

In view of these discrepant opinions we deemed it advisable to reinvestigate this problem and to subject our findings to statistical analysis.

This paper deals with the data of 979 parturient cases in which the mothers' gains and the weights of the newborn infants were recorded and examined to determine the existence, if any, of relationship between them. The cases were collected from the records of private patients who were delivered by members of the obstetric staff at the Beth-El Hospital between Jan. 1, 1942, and Dec. 31, 1943. The case records were examined and the selection of cases was based upon the following criteria:

They were cases of single pregnancies in which the patient began antepartum care before twelve weeks of gestation and was followed regularly to term.

*Presented at a meeting of the Brooklyn Gynecological Society, Oct. 6, 1944.

Onset of labor was spontaneous within fourteen days of the expected date of the confinement; delivery was by the pelvic route with the birth of a normal living infant.

The parturients were normal patients without pre-existing disease and without any disease noted during the antenatal period. A number of them had mild symptoms such as nausea with occasional vomiting, which were corrected. Excess weight gains were noted, in some instances, with evidences of edema. These were not accompanied, however, by any abnormality such as albuminuria or elevation of blood pressure.

Well-balanced diet and fluid balance were stressed and occasionally vitamin supplements were administered. No attempt was made, however, to administer treatment with special diets. The data will be shown in Table I and Fig. 1.

TABLE I. MOTHER'S GAINS AND WEIGHTS OF BABIES (TOTAL GROUP A—979 CASES)

MOTHER'S GAINS IN POUNDS*	AVERAGE WEIGHT OF BABY		BABIES (NO.)	MALES (NO.)	FEMALES (NO.)	AVERAGE WEIGHT OF MALE		AVERAGE WEIGHT OF FEMALE	
	(LB.)	(OZ.)				(LB.)	(OZ.)	(LB.)	(OZ.)
0 to 5	6	8	8	4	4	6	12	6	4
5 to 10	7	5	26	11	15	7	12	7	
10 to 15	6	13	83	46	37	6	15	6	11
15 to 20	7	1	237	115	122	7	2	7	1
20 to 25	7	3	312	168	144	7	5	7	
25 to 30	7	5	201	103	98	7	5	7	
30 to 35	7	6	78	42	36	7	7	7	6
35 to 40	7	12	24	13	11	7	14	7	9
Over 40	8	2	10	5	5	8	2	8	2

*0 pounds up to but not including 5 pounds, etc.

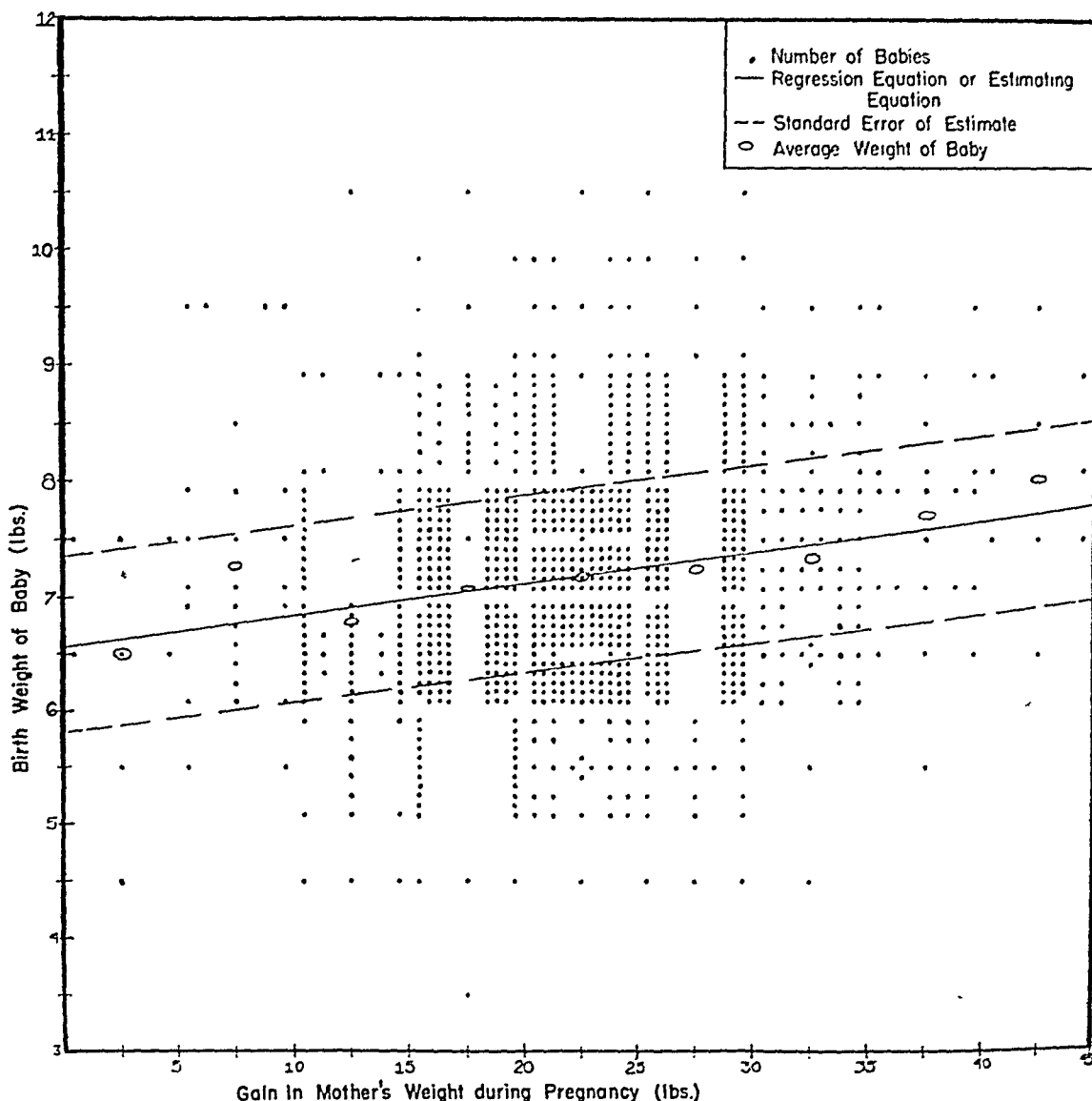
Table I shows the distribution of 979 cases according to mothers' gains in groups of 5 pounds ranging from 0 to 40 pounds and over. Each group contains the average weight of the newborn infant, the number of babies, male and female, and the average of both groups.

The table indicates that there is a progression in the increase of the average weights of the newborn infant. This parallels the mothers' gains during pregnancy. There is one exception, representing 26 cases of the group of mothers' gains 5 to 10 pounds. This correlation does not follow when comparison is made with male and female separately.

Fig. 1 contains the pertinent data of Table I and illustrates graphically the relationship between mothers' gains and weight of the babies at birth. The base line represents the gain of weight of mothers in 5-pound class intervals; the vertical axis, the weights of babies; each dot represents one case and there are 979 cases charted. The circles indicate the average weight of the babies of each group of mothers' gains. The average gain in weight of the mother, which is 22.28 pounds, and the average weight of the baby, 7 pounds, 3 ounces seem to fall in the same class interval.

The solid black line representing the line of the estimating equation and the broken lines representing the plus and minus variation of the standard error of estimate were derived by mathematical formulas. The plus and minus variation was found to be 0.9 pounds.

It would indicate that every 1-pound gain in mother's weight is accompanied by 0.25 pound increase in baby's birth weight. There is a 68 per cent probability that when a baby's birth weight is estimated from mothers' gain in weight, the actual baby's weight will fall within the plus and minus 0.9 pounds of the estimated value.



Graph I RELATIONSHIP OF MATERNAL WEIGHT-GAIN & WEIGHT OF NEWBORN

Fig. 1.

Analysis of Fig. 1

r = Coefficient of correlation = .184928

r^2 = Coefficient of determination = .034198 expressed in a percentage

Y_c = Estimating equation = $6.636317 + .025154 x$

S_y = Standard error of estimate = .910803

x = Mother's gain in weight during pregnancy

y = Baby's birth weight

R^2 , the coefficient of determination represents the percentage of the original variability in "y," that is attributable to the influence of "x" on "y" when it is assumed that that influence is linearly exerted.

Knowing the gain on the mother's weight, the *estimating equation* makes it possible to estimate the birth weight of the baby. Naturally a question arises concerning the accuracy of the estimate—this is answered by the *standard error of estimate* (S_y), on the following terms:

$Y_c \pm 1 S_y$ —has a 68.26 per cent probability of including the actual y

$Y_c \pm 2 S_y$ —has a 95.45 per cent probability of including the actual y

$Y_c \pm 3 S_y$ —has a 99.73 per cent probability of including the actual y

The foregoing is based on the assumption that both x and y are normally distributed. To illustrate the foregoing—assume that the mother's gain in weight was 30 pounds. Substituting this for x in the estimating equation, we have $Y_c = 6.6363 + .0252(30)$. Therefore $Y_c = 7.3909$. Thus we would estimate the baby's weight as 7.39 pounds. The standard error

of estimate is .9108 pounds, therefore there is a 68 per cent probability that the baby's weight will fall within the limits of 7.3909 pounds \pm .9108 pounds. That is, between 6.4801 and 8.3017 pounds. Similarly, there is a 95 per cent probability that the baby's weight will fall between the limits of 7.3909 + 2(.9108) or 7.3909 \pm 1.8216 or specifically between the 5.5693 and 9.2125 pounds. In similar fashion there is a 99.73 per cent probability that the baby's weight will fall between 4.6585 and 10.1233 pounds.

Significance of $r = .184929$

It is practically certain that the population r fell within the limits—.184928 \pm .095928, or + .089000 to +.280856.

Therefore the hypothesis that a sample r of .184928 obtained from a sample of 979 observations could have been obtained from an uncorrelated parent population must be rejected. This sample r is definitely significant!

Stander and Pastore⁸ considered the mother's gain per se of slight significance. They believed that specific weight change, expressed in percentage, was the true index of the mother's gain. This was capable of comparison with norms established by them for small (40 kg.), medium (60 kg.), and large (80 kg.) women. Their curves of weight change during pregnancy would indicate that the heavier the patient, the more marked was her gain. Bray,⁹ in reviewing the literature, notes that a number of observers reported that heavy women gained more than light women. The results of his studies failed to substantiate earlier opinions that body build had an effect upon the increase of weight during pregnancy. Only McIlroy and Rodway⁵ showed the reverse, namely, that heavy patients showed less gain in weight than those of lighter build. Four of their patients who failed to gain weight were large women weighing over eleven stones* (154 pounds).

It has long been generally believed that large women gain more during their pregnancy and tend to bear heavier babies. To test these statements we have grouped the extremes in weights of our cases, those weighing 100 pounds or less, and 175 pounds or more, before pregnancy. The results are indicated in Tables II and III.

TABLE II. COMPARISON OF MOTHER'S GAINS AND WEIGHTS OF BABIES OF TOTAL AND SPECIAL MOTHER-WEIGHT GROUPS

GROUP	AVERAGE MOTHER'S GAIN IN POUNDS	AVERAGE WEIGHT OF BABY		BABIES (NO.)	MALES (NO.)	FEMALES (NO.)	AVERAGE WEIGHT OF MALE		AVERAGE WEIGHT OF FEMALE	
		(LB.)	(OZ.)				(LB.)	(OZ.)	(LB.)	(OZ.)
A*	22.28	7	3	979	507	472	7	5	7	
B†	23.13	6	9	26	11	15	6	7	6	11
C‡	19.25	8		40	19	21	8	2	7	15

*Group A represents total of 979 cases.

†Group B includes mothers weighing 82 to 100 pounds before pregnancy.

‡Group C includes mothers weighing 175 to 252 pounds before pregnancy.

1. The average gain in light women was greater than that of the entire group.

2. The average gain in heavier women was less than that of entire group and that of light women.

3. The average weight of baby was greater in heavier women than the weight of the entire group and light women.

Two facts are suggested by Tables II and III, namely:

1. The gains during pregnancy of heavier women are not greater than those at the other extreme in weight.

2. Heavier women tend to bear heavier babies.

*Stone is equivalent of 14 pounds.

Table III shows a comparison of babies' weights of light and heavy women with similar gains during pregnancy.

TABLE III. RELATION OF MOTHER'S GAIN AND WEIGHT OF BABY IN SPECIAL GROUPS OF MOTHER'S WEIGHTS BEFORE PREGNANCY

GROUP B				GROUP C			
MOTHERS WEIGHING 82 TO 100 LB.				MOTHERS WEIGHING 175 TO 252 LB.			
MOTHER'S GAINS IN POUNDS*	AVERAGE WEIGHT OF BABY		BABIES (NO.)	MOTHER'S GAINS IN POUNDS*	AVERAGE WEIGHT OF BABY		BABIES (NO.)
	(LB.)	(OZ.)			(LB.)	(OZ.)	
0 to 5				0 to 5	7	8	2
5 to 10				5 to 10	7	13	3
10 to 15	7	8	1	10 to 15	8	6	7
15 to 20	6	6	7	15 to 20	8	5	10
20 to 25	6	5	8	20 to 25	8	6	8
25 to 30	6	15	7	25 to 30	7	13	6
30 to 35	6		2	30 to 35	8		2
35 to 40	6	8	1	35 to 40	8	8	2

*0 pounds up to but not including 5 pounds, etc.

Summary and Conclusion

The relationship between mother's weight gain and the weight of the baby at birth has been examined from the data of 979 parturient cases. The average mother's gain was 22.28 pounds; the average weight of the baby was 7 pounds, 3 ounces.

There is correlation between the weight gain of the mother and the weight of the baby at birth. Although the degree of correlation is low, it is nevertheless significant. There is a 68 per cent probability that the baby's birth weight can be predicted on the basis of the mother's gain, within a range of plus or minus 0.9 pound of the estimated figure.

The size of the mother influences the weight gain during pregnancy. The light women show a larger gain. The heavier women show a smaller gain than the light. Heavier women tend to bear heavier offspring.

We are indebted to Harold Stein, B.S.S., M.B.A., Instructor in Economics, Brooklyn College, Brooklyn, N. Y., for assistance in the statistical analysis.

References

1. Davis, C. H.: AM. J. OBST. & GYNEC. 6: 575, 1923.
2. Slemmons, J. H., and Fagan, R. H.: AM. J. OBST. & GYNEC. 14: 159, 1927.
3. Bingham, A. W.: AM. J. OBST. & GYNEC. 23: 38, 1932.
4. Hanley, B. J.: West. J. Surg. 42: 251, 1934.
5. McIlroy, A. L., and Rodway, H.: J. Obst. & Gynaec. Brit. Emp. 44: 221, 1937.
6. Cummings, H. A.: AM. J. OBST. & GYNEC. 27: 808, 1934.
7. Toombs, P. W.: AM. J. OBST. & GYNEC. 22: 851, 1931.
8. Stander, H. J., and Pastore, J. B.: AM. J. OBST. & GYNEC. 39: 928, 1940.
9. Bray, Philip, N.: AM. J. OBST. & GYNEC. 35: 802, 1938.

FATAL HEMORRHAGE FROM AN ANGIOMATOUS POLYP OF ILEUM COMPLICATING PREGNANCY

S. H. POLAYES, PH.B., M.D., AND THOMAS F. NEVINS, M.D., BROOKLYN, N. Y.
(From the Departments of Pathology and Obstetrics, Prospect Heights Hospital, and the
Department of Pathology, Cumberland, Hospital)

THE literature to date contains reports of approximately 93 cases of angioma of the gastrointestinal tract. The most masterful review of the subject was written by Kaijser¹ in 1936. For a complete bibliography up to that time the reader is referred to his publication. Kaijser collected and classified in table form 74 cases of angioma of the gastrointestinal tract, of which 8 occurred in the ileum. In 1940 Pierose² reviewed the cases which had been published since Kaijser's review, and reported a case of his own, bringing the total to 84. Since then, cases reported by Hunt,³ Morton,⁴ White,⁵ Stajano,⁶ Gladden,⁷ and Christopher⁸ have brought the complete total to date to 93. Of these, in about 13 cases, the lesion occurred in the ileum. In most of these, the angioma was one of several similar lesions coexisting in other segments of the intestines, especially in the jejunum. In very few of these instances was the lesion solitary and limited to the ileum. Kaijser, in his discussion, emphasized the desirability of reporting every case in order to amplify our knowledge of the condition. The case reported in this publication presents a feature which, as far as the author could determine, was not present in any of the previously reported cases, and hence the only one of its kind in the literature to date. It was therefore considered worthy of publication.

Case Report

M. C., aged 26 years, Irish-American housewife, 6 months pregnant, was admitted to the Prospect Heights Hospital on Sept. 3, 1943, suffering from severe secondary anemia which resulted from repeated attacks of rectal bleeding. The bleeding episodes began in February, 1942, six months following her first pregnancy, and had become worse with the onset of her present pregnancy.

The patient's past history disclosed that she had had scarlet fever in childhood and Bright's disease thirteen years ago. About seven years ago, her tonsils were removed. Menses began at the age of 15 years and were irregular and prolonged, each period lasting about seven days. Her first pregnancy terminated in a full-term stillbirth on December 14, 1941. It was believed to be due to a complicating hypertension with edema. This condition, however, subsided post partum. At that time she also had a marked anemia, the red cell count having been 3,690,000 per cubic millimeter and the hemoglobin 43 per cent (Newcomer).

On admission to the hospital her pulse was 70 and respirations 23 per minute. The temperature was normal. She showed all the signs and symptoms of an extremely severe anemia. There was a distinct hemie murmur. The abdomen showed an enlarged uterus corresponding to six months' gravidity. There was active bleeding per rectum, where a mass was allegedly palpable at the ampulla recti.

The laboratory data was as follows:

Blood Count:

Red blood cells— 1,570,000 per c.mm.

Hemoglobin — 30 per cent (Newcomer)

White blood cells— 9,250 per c.mm. of which 88 per cent were polynuclear cells and 12 per cent lymphocytes.

Blood grouping tests showed her to be a group O, Rh positive.

Blood chemistry showed a creatinine of 1.8 mg. per cent.

Urinalysis was essentially normal. The specific gravity was 1.038, reaction acid, faint trace of sugar, albumin and acetone negative. The sediment consisted of an occasional red blood cell and about 5 white blood cells per high-power field.

The patient was given intravenous glucose and saline and treated for impending shock. During the night, the nurse reported that the fetal heart sounds could not be heard. While preparations were being made for a blood transfusion, a massive hemorrhage per rectum occurred, and the patient expired before the blood transfusion could be performed.



Fig. 1.—Photomicrograph of skin nevus from foot, showing the ovoid clusters of pigmented nevus cells (arrow) in papillae of cutis, lying between deeply pigmented rete pegs (X130).

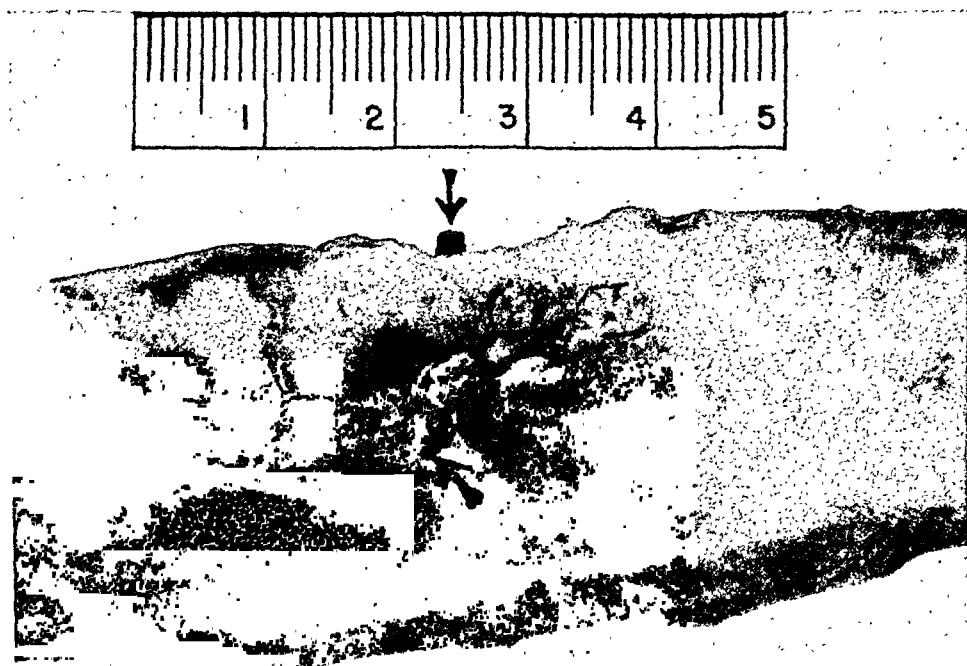


Fig. 2.—Gross specimen of opened ileum showing mucosal surface with area of ulceration and angiomatous polyp projecting into the lumen. Note blood clot covering free end of polyp (arrow). The arrow between ruler and ileum shows the mesenteric artery (from which the angioma arises) entering the wall of the gut.

Postmortem Examination.—General description: The body was that of a fairly well-developed and well-nourished young white woman. The skin and mucous membranes were pale. There was a generalized subcutaneous pitting edema of the extremities. There were numerous brown to blue-black pigmented flat nevi, diffusely scattered over the entire skin, and especially marked on the legs and feet. The microscopic examination of these nevi showed them to be of the benign pigmented type (Fig. 1).

Cavities: The pleural, pericardial and peritoneal cavities were normal.

Cardiovascular system: The heart weighed 225 grams. It was essentially normal except for microscopic evidence of a mild degree of myocardial degeneration.

Respiratory system was entirely normal.

Gastrointestinal system was normal down to a point in the ileum about 50 cm. above the ileocecal junction. From this point down to the rectum the intestines were distended with fluid and clotted blood which was visible through the wall of the gut. Near the upper level of the column of blood, a mesenteric vessel of relatively large caliber was found entering the wall of the ileum and leading to an area of superficial ulceration in the mucosa, about 1.5 cm. in greatest dimension. From the center of this ulcerated area there projected a soft, polypoid structure about 0.8 cm. in length, and covered with fresh blood clot (Fig. 2). The mucosa surrounding the base of the polyp showed a finely nodular thickening.

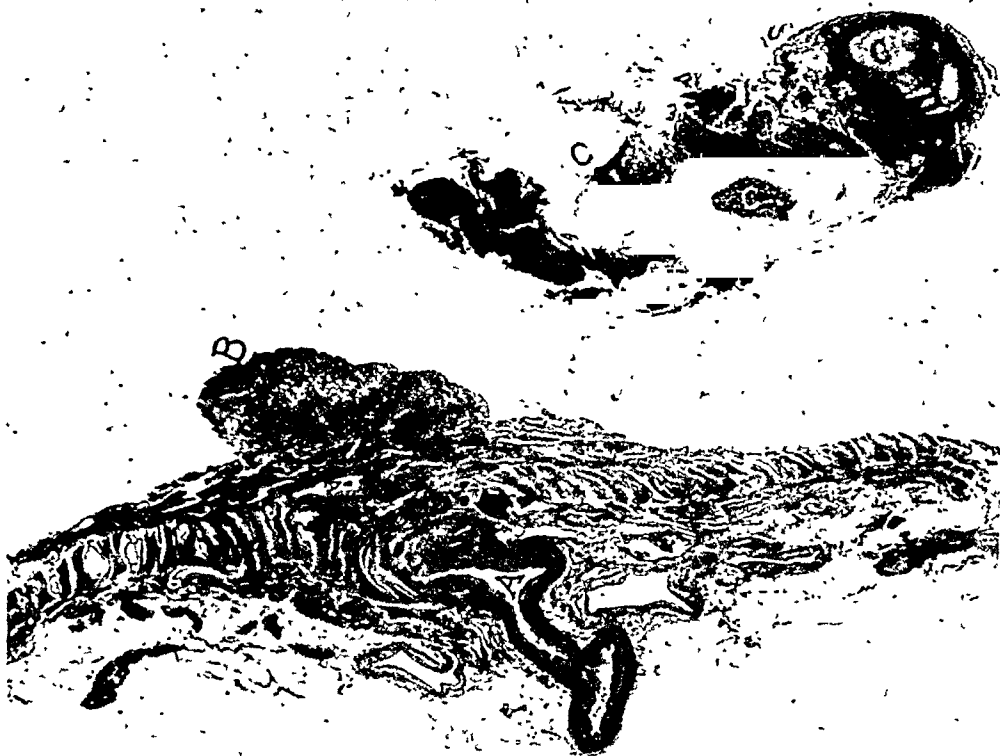


Fig. 3.—Low-power magnification of ileum at site of polyp. Note the large caliber of the artery (A) as it courses through the wall of the gut to the mucosa where it branches (A') out to form the angiomatous polyp (B). The thrombotic mass (C) which covered the free end of the polyp has been detached. ($\times 10$.)

Microscopic section of this portion of ileum showed the mesenteric vessel entering the wall to be of a relatively large caliber throughout its course. (Fig. 3). Within the wall of the ileum it divided into branches which formed congeries of vessels, assuming the characteristic architecture of capillary angiomatous. These lesions were found in the serosal, muscular, and mucosal layers. In the latter they gave rise to the polyp described in the gross. The polyp was composed of numerous blood capillaries, the endothelial cells of which were hyperplastic and large. It had penetrated the mucosa and showed a secondary inflammatory process with ulceration of its surface. Here it was partly covered with fresh thrombus deposits, the major portion of which had been detached during the gross examination of the specimen (Fig. 4). Some of the angiomatous within the wall of the ileum occurred as discrete nodules which invaginated into the sinuses lined by hyperplastic endothelial cells. In areas the degree of endothelial proliferation in the capillaries was so pronounced as to suggest a possible angio-endotheliomatous change (Fig. 5). There was, however, no definite evidence of malignancy in any of the angiomatous. Throughout the submucosa, as well as in the muscularis and serosa, were found numerous dilated but empty sinuses which distorted the normal architecture of those areas, forming huge gaps between muscle bundles and between submucosa and muscularis.

The rest of the gastrointestinal tract, including the appendix, mesentery, and omentum were essentially normal. The pancreas weighed 60 grams and showed no changes.

Biliary system: The liver weighed 1,480 grams and showed no changes. The gall bladder, cystic duct, common duct, and ampulla of Vater were normal.

Urinary system: The right kidney weighed 120 grams and the left kidney 105 grams. They were normal. The ureters, bladder, and urethra were normal.

Genital system: The external genitalia were normal. The uterus contained a normally developed dead female fetus of six months' gestation. The placenta was normally implanted and showed no changes. The umbilical cord was normal. The myometrium was very pale and edematous. The Fallopian tubes and ovaries were normal.

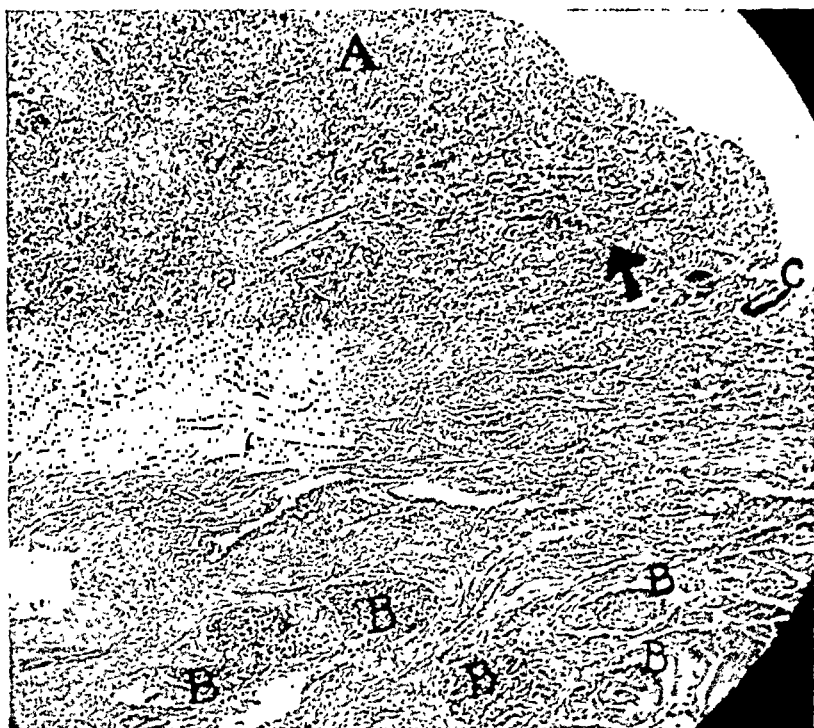


Fig. 4.—Section through the polyp (A) including underlying wall with its capillary angiomata (B) and ulceration of the mucosal lining (C). Note the myriads of capillaries in the polyp and the inflammatory infiltrate within it (arrow). (X70.)

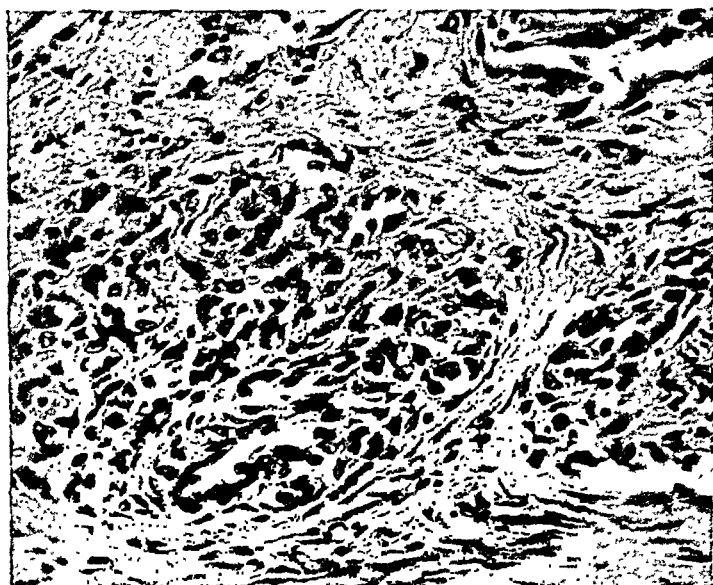


Fig. 5.—Higher magnification of the angiomata in the wall of the ileum shown in Fig. 4. Note the marked endothelial proliferation of the capillaries of the angiomata and the endothelium-lined spaces in which they are found. (X300.)

Lymphatic system: The thymus weighed 12 grams and showed no changes. The spleen weighed 140 grams and showed hypertrophy of follicles. The sinuses were almost completely devoid of blood. A small splenulus in the gastrosplenic ligament showed similar changes.

Anatomic Diagnosis:

1. Angiomatous polyp of ileum, with ulceration and hemorrhage.
2. Massive intestinal hemorrhage.
3. Secondary anemia.
4. Subcutaneous edema.
5. Gravid uterus (six-month female fetus).
6. Follicular hyperplasia of spleen and splenulus.
7. Multiple benign pigmented nevi of skin.

Discussion

Detailed discussion of the general subject will not be attempted here. This was already admirably done in the publications previously mentioned. A few of the more pertinent facts will be mentioned in relation to the present case. Bleeding vascular lesions of the gastrointestinal tract may be due to telangiectasia (local or as an expression of a general diathesis), varicosities, or true neoplasms. The latter include cavernous angioma, capillary angioma, and angio-endothelioma. Grossly the lesions may manifest themselves in the form of ulcers (the polyp may be unnoticed), fungating bulky masses projecting into the lumen, or strictures. The present case is one of a true neoplasm involving all layers of the portion of ileum affected. In fact, in some sections, as was already indicated above, the neoplasm assumed features suggestive of an endothelioma which is a malignant lesion. The process was a local one, no other angiomas having been found elsewhere. At this point it may be of interest to note that there was a marked tendency to nevus formation in the skin. This may have some relationship to the capillary angioma in the ileum, since many of the skin nevi are capillary angiomas. Clinically it was noted that the pigmented nevi of the skin became more accentuated and increased in number with pregnancy. It is conceivable that the state of gravidity activated the angioma as well as the skin nevi. Kaijser makes mention of the fact that in one of his cases of angioma of the stomach, bleeding increased with puberty, and he mentioned puberty and gravidity among the endogenous stimuli which may activate the development of angiomas. He also cites, as a case in point, the case of Blaschko's in which the angioma followed pregnancy.

The fact that in this case the lesion complicated pregnancy makes it unique and adds to its importance. No other such instance has been found in the literature. It is quite probable that intestinal bleeding due to an angioma of the tract occurs more commonly in pregnancy than is supposed, but is overlooked because the bleeding is inconsequential and ceases with termination of the pregnancy. It will be noted that in this case the patient's previous pregnancy (about two years prior to the recent one), terminated in a stillbirth, the patient showing a profound anemia at the time, with a hemoglobin of only 43 per cent. It is quite likely that she had had intestinal bleeding episodes with the first pregnancy also, but they probably went unnoticed because they were not massive enough to attract her attention, and the absence of vaginal bleeding probably gave her physician a false sense of security, so that more strenuous efforts to determine the cause of the anemia were not made.

The matter of diagnosis, naturally, is of prime importance, since recent experiences have shown that the condition is amenable to surgery and cure, if the lesions are not too diffuse or multiple.^{2, 5, 8} In some instances x-ray may be of aid in diagnosis,⁹ but even in the absence of positive x-ray findings, unexplained intestinal bleeding of a degree sufficient to produce an anemia should be considered a definite indication for exploratory laparotomy to exclude an

operable angioma of the intestines. In this case, as has been found to be also true in others, the large offending artery shown in the specimen could serve as a guide to the location of the lesion, and the level of the blood in the lumen of the gut, visible as it was through the wall, could indicate the source of the bleeding. Although, in the present case, surgical intervention was impossible upon admission to the hospital, because of the massiveness of the hemorrhage, it is possible that had the diagnosis been made earlier in her course, surgery might have spared her life.

Summary

1. A unique case of fatal hemorrhage from an angiomatous polyp of the ileum complicating pregnancy is reported. No similar case complicating pregnancy was found in the literature.

2. A brief review of the subject of angioma of the gastrointestinal tract reported to date shows a total of 94 cases including the author's case. Of these, only about 13 cases involved the ileum, most of them being cases in which coexisting angiomas were found in other segments of the intestine, especially jejunum. Instances of solitary angiomas of the ileum alone, as in the author's case, are even rarer.

3. A plea is made for early diagnosis of the condition and attempt at surgical intervention.

References

1. Kaijser, R.: Arch. f. klin. Chir. 187: 351, 1936.
2. Pierose, P. N.: J. A. M. A. 115: 209, 1940.
3. Hunt, V. C.: Surgery 10: 651, 1941.
4. Morton, C. B., and Burger, R. E.: Surgery 10: 891, 1941.
5. White, R. J.: South. Surgeon 10: 886, 1941.
6. Stajano, C.: Arch. urug. de med., cir. y especialid. 19: 466, 1941.
7. Gladden, J. R.: Am. J. Surg. 56: 495, 1942.
8. Christopher, F.: Ann. Surg. 116: 945, 1942.
9. Weber, H. M., and Kirklin, B. R.: Am. J. Roentgenol. 47: 243, 1942.

39 AUBURN PLACE.

COCCIDIOIDAL PELVIC INFLAMMATORY DISEASE

ERNEST W. PAGE, M.D., SAN FRANCISCO, CALIF., AND
CAPTAIN L. MORGAN BOYERS, M.C., A.U.S., OAKLAND, CALIF.

(From the Department of Obstetrics and Gynecology, University of California Medical School, San Francisco, and the Gynecology Service of Alameda County Hospital, Oakland)

INFECTION of the female genital tract with *Coccidioides immitis* has been recorded once before.¹ In both cases, surgery has been followed by complete recovery. While Jacobson attributed the recovery of his patient to the use of a coccidioidin vaccine and colloidal copper, ours has regained her health with no "specific" therapy.

Case Report

Mrs. G. L., aged 33 years, entered the Alameda County Hospital on Aug. 30, 1941, complaining of severe lower abdominal pain and fever.

The only significant points in her past history were concerned with her activities in an area known to be endemic for coccidioidomycosis. She had lived only in Portland, San

Francisco, and Los Angeles until 1936, when she began to take annual trips to Tucson, Arizona, where she camped in the surrounding desert country digging for archeological ruins. She was in excellent health until, on one of these trips in 1939, she had a brief illness consisting of nausea, vomiting, and weakness for two weeks. A tubal insufflation was done at this time because of sterility and she was told that her tubes were open.

She remained in Arizona, and her health was good until April, 1941 (four months before entry), when she had pelvic pain, chills, fever, and malaise which persisted for several weeks. These symptoms abated, but six hours before admission, she was awakened by severe lower abdominal pains accompanied by vomiting.

Upon admission, the patient appeared pale, undernourished and in obvious distress, with a temperature of 103.6° F. and a pulse rate of 130. The only pertinent findings were made on pelvic examination. The lower half of the abdomen was distended, rigid, and tender to light touch. The uterus seemed to be of average size and there were ill-defined tender masses in both adnexal regions. The hemoglobin was 9.6 Gm. (57 per cent), red blood cell count was 3,460,000, and leucocyte count 13,200 with 78 per cent neutrophils. The blood sedimentation rate showed a drop of 18 mm. in 11 minutes.

The initial diagnosis was bilateral salpingo-oophoritis and pelvic peritonitis of undetermined etiology. She continued to have a high swinging fever for ten days despite intensive sulfathiazole therapy. A colpotomy was done because of a fluctuant abscess bulging into the cul-de-sac, and a large quantity of greenish pus escaped. This was negative for gonococci on smear and culture, and a guinea pig inoculation was reported after one month as "negative for tuberculosis."

During the next two months, she remained in the hospital with an intermittent fever, a moderate anemia, persistent leucocytosis, and a rapid sedimentation time. On two occasions, the colpotomy wound was reopened because of accumulated purulent material in the cul-de-sac. Sulfathiazole was again administered in two-week courses twice but with no evident influence upon the course of the infection. Finally, on Jan. 7, 1942, she was dismissed with relative freedom from pain and no fever. Because of the repeated exacerbations and the persistence of bilateral tuboovarian masses, she was asked to return for surgery after two months of rest.

On March 1 a laparotomy was performed and the entire visceral and parietal peritoneum was found to be studded with small, white irregular nodules varying from 1 to 3 mm. in size. The appearance of the abdomen and pelvic organs was like that of advanced tuberculous peritonitis. The uterus was slightly enlarged and covered with adhesions. The left tube and ovary were involved in a single cul-de-sac mass, 8 cm. in diameter and containing multilocular abscesses. The right ovary appeared normal, but the right tube was markedly inflamed and thickened, sealed at the fimbriated end, and contained a brown fluid. The left ovary and both tubes were removed and a subtotal hysterectomy was done.

The pathologic report was submitted by Dr. M. R. Oldt. On microscopic examination, the abscess walls consisted of granulation tissue densely infiltrated with plasma cells and occasional eosinophiles and containing tubercle-like lesions composed of epithelioid cells and giant cells of Langhans' type. Sections from the right tube (Figs. 1 and 2) and from the peritoneum showed similar lesions. The involved areas contained globular bodies 50 to 60 micra in diameter with double peripheral membranes. Some of the organisms were filled with endospores. Diagnosis: Coccidioidal granuloma of tubes, ovary, and peritoneum.

The patient had a smooth, afebrile convalescence. Hospitalization was prolonged because of a small draining sinus at the lower angle of the incision. Cultures taken from this sinus, and also from the posterior vaginal fornix showed a growth of *Coccidioides immitis*. Roentgenograms of the chest revealed no lesions or evidence of scarring, and no bony lesions were seen in x-rays of the pelvis.

Coccidioidin skin tests performed five and seven weeks postoperatively were positive in 1:100 dilution, negative in 1:1,000 dilution. Three complement fixation tests on serial dilutions of serum were done during the second month postoperatively, and all were positive through the 1:32 dilution and negative with 1:64 dilutions.

At three, four, and five months after surgery, examinations showed no masses or tenderness in the pelvis and the patient had no complaints. The abdominal and colpotomy wounds healed, and she gained 20 pounds in weight. Her temperature, leucocyte count, and sedimentation rate have remained normal. Ten months after surgery, the serum complement

fixation test was positive in 1:8 dilution and negative in 1:16 dilution. This reduction in titer indicated that the infection was diminishing and coincided with known clinical improvement.

Eighteen months and again two years after surgery, examinations showed normal findings except for a very slightly enlarged but nontender right ovary. Coccidioidin skin tests were repeated with the same results as on the previous examinations. She was now 10 pounds overweight, was working full time in a manufacturing plant, and stated that her general health was excellent.



Fig. 1.—Wall of right tube ($\times 120$) showing tubercles containing *Coccidioides immitis* in giant cells.

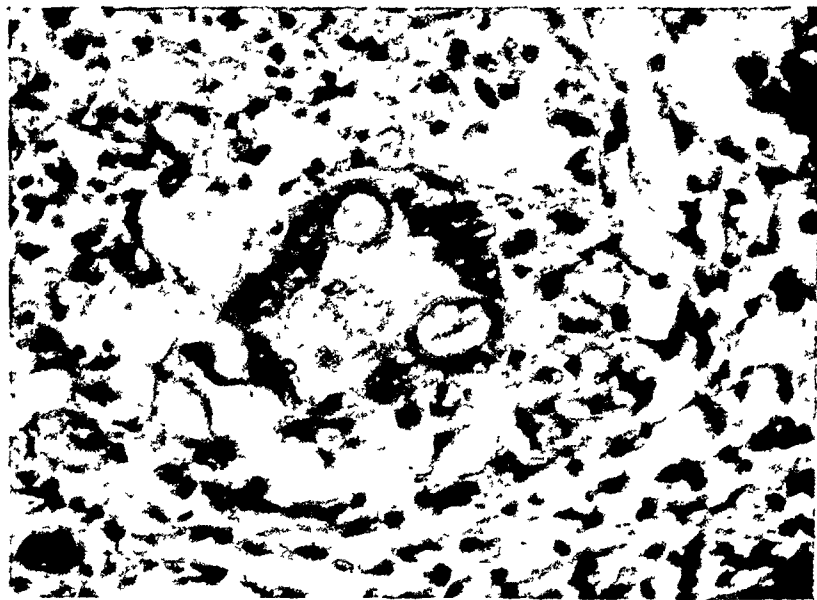


Fig. 2.—Details of a giant cell ($\times 500$) containing three organisms.

Comment

Except for occasional primary skin lesions, the initial route of infection is by inhalation of the coccidioidal chlamydospores which inhabit the soil of certain dry areas in the Southwest. The region near Tucson, Arizona, is known to be an endemic focus² and it is highly probable that this patient acquired her infection while digging ruins in the neighboring desert, at least six months before entry to the hospital. Whether the tubal insufflation had any part in the inoculation or spread of the disease is problematical.

The initial infection is commonly mild, and it has been estimated that only once in 500 to 1,000 cases does the fungus disseminate in this manner.³ That coccidioidal peritonitis itself is unusual is indicated by a report in 1939⁴ of the second case in which the diagnosis was made during life. The infection occurred in a man who died one month later.

The precise factors which determined the favorable outcome in our case are not known. It is very unlikely that the administration of sulfonamides influenced the course of her illness. Surgical extirpation of the heavily infected pelvic organs undoubtedly favored recovery, but her immunologic defense must have been high at that time.

Summary

A case is reported of disseminated coccidioidomycosis involving primarily the uterus, tubes, and one ovary. Surgical removal of these organs was followed by a complete cure.

Appreciation is expressed to Dr. C. E. Smith and Miss R. J. Wheatlake of the Department of Public Health and Preventive Medicine, Stanford University School of Medicine, for their assistance in the coccidioidin and serologic tests; and to Miss Ida May Stevens, Supervising Morbidity Statistician, Bureau of Epidemiology, for her review of the coccidioidal granuloma cases reported to the California State Department of Public Health.

References

1. Jacobson, H. P.: *M. J. & Rec.* 130: 424, 1929.
2. Farness, O. J.: *J. A. M. A.* 116: 1749, 1941.
3. Smith, C. E.: *M. Clin. North America* 27: 790, 1943.
4. Ruddock, J. C.: *J. A. M. A.* 113: 2054, 1939.

GONORRHEAL ARTHRITIS COMPLICATING PREGNANCY TREATED WITH PENICILLIN

CARL HENRY DAVIS, M.D., WILMINGTON, DEL.

GONORRHEAL arthritis in women is relatively rare. Salberg and Brunet reported (1940) that in the Women's Division of the Public Health Institute of Chicago only thirty cases were observed in the years from 1931 to 1938, an incidence of 1 in 200 of the women treated for gonorrhea. Gonorrheal arthritis appears to be an extremely rare complication of pregnancy, or at least one that has rarely been reported in the literature. Few textbooks on obstetrics mention this complication; Royston, in 1923, reported four cases of gonorrheal arthritis during pregnancy; de Sa Pereira, Uvalde, in 1936, reported a very severe case of gonococcal polyarthritis and discussed the efficacy of vaccinotherapy; Upton, 1938, added another case report with a discussion of the general problem; and Mengert and Paul, 1942, reported the cure of three cases late in pregnancy in a discussion of the effects of artificial pyrexia on pregnant women. The case to be reported appears to be the first treated with penicillin.

Case Report

1944, she reported at the office complaining of very severe pain in her right arm, and she was sent to the Delaware Hospital for observation. On admission, her temperature was 99.6° F., but thereafter it was normal. Her history taken at the time indicated that she had a slight vaginal discharge but there were no symptoms suggestive of gonorrhea. Neither smears nor cultures were made at this time. On the third day she was permitted to return home under the care of her family physician who started large doses of vitamin B. A diagnosis of neuritis was recorded on the hospital record. On July 5 she was seen at my office, but the skin of the wrist was so badly blistered from the use of tincture of iodine that an examination was not possible. She was next seen on July 20, when it was found that she had a marked deformity of the right wrist. She was sent back to Delaware Hospital for x-ray examination and treatment. Dr. Lattomus found: "Advanced decalcification of the carpal bones with destruction of many of the articulating surfaces; this is particularly true of the distal articulating surfaces of the radius. There is a dorsal subluxation of the ulna. Diagnosis: Infectious arthritis. Gonorrhea should be ruled out."



Fig. 1.—The wrist, on July 20, 1944, showed marked decalcification and destruction of many of the articulating surfaces. There was a dorsal subluxation of the radius shown on a lateral plate.

The original smears were negative but the gonococcus was grown in the cultures. As soon as the diagnosis of gonorrheal arthritis was established, 20,000 units of penicillin were administered intramuscularly five times daily until she had a total of 1,000,000 units. Smears taken after 500,000 units were negative, and a culture after 600,000 units was negative. On admission to the hospital the wrist was supported with a light plaster splint which permitted free movement of the fingers. Within a few days the swelling and pain disappeared and the patient was permitted to move her wrist freely. A blood calcium determination

made on July 22 showed only 8.5 per cent, and thereafter she was given 60 grains daily of dicalcium phosphate compound with viosterol. It is possible that this aided in her recovery. She went into labor spontaneously on Aug. 7, 1944. The labor and puerperium were uneventful. Her temperature remained under 99° F. during her entire stay in the hospital. Re-examination of the involved wrist two days before she left the hospital showed "complete disappearance of the infectious process. Many of the articulating spaces are still preserved. There is, however, a destruction of the distal articulating surface of the radius with the same dorsal displacement of the ulna as seen in the examination of July 20, 1944." The patient now has a very serviceable wrist but there is still the same displacement of the ulna.



Fig. 2.—The wrist, on August 11, just before discharge from the hospital, showed a complete disappearance of the infectious process and a considerable degree of restoration with preservation of many of the articulating surfaces.

Discussion

Gonorrhea is such a rare finding among my private patients that I did not suspect that it was the cause of the trouble in this case. However, after the diagnosis was made, the husband admitted that he was under treatment for an infection. Furthermore, the smears were all negative and it was only through the cultures that the x-ray diagnosis was established as correct. The x-ray findings in gonorrheal arthritis seem to be quite typical and this aid should be obtained whenever a painful joint develops.

A review of the cases reported in the literature indicates that gonorrheal arthritis is most likely to develop during the third trimester of pregnancy. The arthritis also develops usually during the subacute or chronic stage of the local infection rather than during the acute stage.

Gonorrheal arthritis may be monoarticular or polyarticular. It has been stated that the gonococcus has a predilection for the upper extremi-

ties in women and for the lower ones in men. In the thirty cases reported by Salberg and Brunet, the joints attacked were: wrist, seven cases; knee, wrist, one case; shoulder, wrist, two cases; shoulder, foot, one case; shoulder, hand, one case; shoulder, wrist, ankle, one case; knee, ankle, two cases; knee, wrist, two cases; knee, finger, toe, one case; foot, wrist, two cases. The wrist alone or with other joints were involved fifteen times, or in one-half of all cases.

Mengert and Paul have demonstrated that artificial pyrexia may be used safely during pregnancy for the treatment of arthritis. Use of large doses of sulfonamides during pregnancy does not appear rational owing to the known toxicity of these drugs. Penicillin promises prompt cure of gonorrhea without any apparent untoward effects. The seriousness of gonorrheal arthritis complicating pregnancy would seem to justify using a dose of penicillin large enough to insure a cure. It is probable that a smaller dose than the one used in this case would have been adequate.

References

- Royston, G. D.: *AM. J. OBST. & GYNEC.* 5: 512, 1923.
 de Sa Peretra, Urvald: *Hospital, Rio de Janeiro* 8: 889, 1936.
 Upton, J. R.: *California & West. Med.* 48: 326, 1938.
 Salbert, J. B., and Brunet, W. M.: *M. Rec.* 152: 294, 1940.
 Mengert, W. F., and Paul, W. D.: *AM. J. OBST. & GYNEC.* 44: 702, 1942.

REDUCING PROPERTIES OF THE CHORIONIC GONADOTROPIC HORMONE AS RELATED TO THE CHEMICAL DETERMINATION OF PREGNANCY

DONALD E. BOWMAN, PH.D., INDIANAPOLIS, IND.

(From the Indiana University School of Medicine)

MELLO¹ has recently described a procedure for the chemical determination of pregnancy in which a urinary reducing factor which is assumed to be the chorionic gonadotropic hormone is separated from urine and is estimated by determining its ability to reduce a sugar reagent. Since the influence of urinary glucose was not described, an account of such observations may be desirable along with a brief discussion of earlier observations regarding reducing factors in relation to pregnancy determination.

Experimental

In the procedure described by Mello¹ the reaction of the urine is adjusted to pH 4 with acetic acid, and the reducing fraction is adsorbed on kaolin. After eluting with 0.1 N sodium hydroxide and centrifuging, the reducing power of the eluate is estimated by Somogyi's sugar method.² This is expressed in terms of the difference between a blank titer and the titer required by the eluate and is a measure of the reducing fraction derived from 1 c.c. of urine. Values obtained in this manner and exceeding 1.6 c.c. have been included in the range of a positive pregnancy reaction.

In the present study, varying amounts of glucose were added to nonpregnancy urine which was then treated according to this procedure. From the data presented in Table I it is apparent that small quantities of urinary glucose are sufficient to significantly alter the results. In this series the urine glucose appearing in the eluate varied between 7 and 40 per cent of the added sugar, this percentage gradually decreasing with an increase in the concentration in the urine. It may be observed that in this case the addition of 0.1 per cent glucose is sufficient to bring the total reducing fraction of the eluate within the range ascribed to pregnancy.

TABLE I. INFLUENCE OF URINARY GLUCOSE UPON THE RESULTS

AMOUNT OF GLUCOSE PRESENT (%)	REDUCING POWER PER C.C. OF URINE IN TERMS OF 0.005 N SODIUM THIOSULFATE (C.C.)
0.0	0.58
0.005	0.71
0.01	0.97
0.03	1.11
0.05	1.27
0.05	1.395
0.1	1.925
0.2	2.58
0.3	2.63
0.5	3.20

TABLE II. SUMMARY OF RESULTS WITH URINE SPECIMENS

		SPECIFIC GRAVITY	REDUCING POWER PER C.C. OF URINE IN TERMS OF 0.005 N SODIUM THIOSULFATE (C.C.)
Nonpregnancy	Average	1.024	1.54
	Maximum	1.045	3.45
	Minimum	1.006	0.20
	(Per cent false: 42)		
Pregnancy	Average	1.021	1.25
	Maximum	1.030	3.00
	Minimum	1.013	0.30
	(Per cent false: 38)		

Since this concentration of urinary reducing substances expressed as glucose is not unusual in normal urine, eluates were prepared from a number of such nonpregnancy specimens in order to determine whether such materials might interfere following the use of kaolin. It was found that in 42 per cent of fifty cases the reducing power of the prepared eluates was sufficient to exceed the limit ascribed to pregnancy. Such specimens gave a negative test with Benedict's qualitative sugar reagent. On the other hand, the variation in the reducing materials in fifty pregnancy specimens was sufficient to give values below that assigned to pregnancy in 38 per cent of fifty cases. It would therefore appear that the reducing agents present in normal urine are of sufficient magnitude and vary enough to seriously interfere with the use of the procedure.

Discussion

Since the use of a sugar reagent occurred to Mello after following some of our earlier studies on reducing factors as related to the determination of pregnancy, a brief discussion of some of these earlier findings and certain conclusions which have been drawn may be of interest. While dealing with carbohydrates in biologic solutions, it was observed by Visscher and Bowman that a characteristic type of precipitate, apparently not related to the presence of a simple carbohydrate, forms when pregnancy urine is treated under certain conditions with phenylhydrazine.³ Following a brief account of these observations, numerous reports indicated that the correlation with pregnancy is not sufficient to warrant its use as a test.¹⁻⁹ On the other hand, others reported that with certain precautions considerable accuracy could be obtained.¹⁰⁻¹⁴ A gradual decline in the reaction following delivery was reported¹³ and positive reactions were observed with added gonadotropin.¹¹⁻¹³

Frech applied the reaction in 513 cases in one series and reported about 92 per cent accuracy;¹⁴ however, in a subsequent series he obtained a much lower percentage of correct results.¹⁵ Our own experience in part parallels that of Frech. In a second laboratory employing new reagents and known specimens,

it immediately became apparent that there was marked contrast between this second series and the initial one which, to a large degree, consisted of unknowns.

In view of this and the negative reports, it was concluded that the reaction is not suitable or not sufficiently well defined. Therefore, some attention was directed toward the investigation of specific reactions which might account for the mechanism, and consideration was given to reducing properties of the chorionic gonadotropic hormone. At that time the carbohydrate content of this hormone had not been established and interest was turned in particular to its rather unusual properties of taking up iodine at a greatly increased rate in the presence of a relatively large amount of phosphate buffer salts at moderately elevated temperature.¹⁶

This behavior was traced to the phenolic groups present in the hormone and in nearly all proteins.¹⁷ In one series of normal specimens free of detectable protein, it was found that pregnancy and nonpregnancy specimens could be differentiated.¹⁸ Similar findings have been reported by Mello.¹⁹ Nevertheless, while the reaction is quite sensitive, the presence or variations of minute quantities of ordinary proteins would obviously interfere. Numerous attempts at separating the desirable and undesirable fractions were made without success, employing procedures which might be practical in routine work.

Therefore, from these considerations and from the data briefly presented here, it must be concluded that at present a suitable means for the chemical determination of pregnancy based upon the reducing properties of gonadotropin, if feasible, has not as yet been adequately defined. However, it is believed that a study of the phenolic reaction first observed in this work may have wider application in view of the functional dominance of this radical in a number of hormones, enzymes, and proteins of disease.

References

1. Mello, M. I.: *Rev. brasil. de biol.* 3: 119, 1943.
2. Somogyi, M.: *J. Biol. Chem.* 117: 771, 1937.
3. Visscher, J. P., and Bowman, D. E.: *Proc. Soc. Exper. Biol. & Med.* 31: 460, 1934.
4. Belonoschkin, B.: *Zentralbl. f. Gynäk.* 61: 2797, 1937.
5. Messinger, W. J., Presberg, M. H., and Fellows, M. D.: *AM. J. OBST. & GYNEC.* 35: 295, 1938.
6. Bodo, B.: *Orvosi hetil.* 81: 11, 1937.
7. Frankl, O., and Engel, P.: *Zentralbl. f. Gynäk.* 60: 2645, 1936.
8. Ostadal, B.: *Zentralbl. f. Gynäk.* 61: 266, 1937.
9. Dodds, G. H.: *Brit. M. J.* 2: 244, 1936.
10. Menken, J. G.: *Nederl. tijdschr. v. geneesk.* 79: 979, 1935.
11. Dölff, C.: *Zentralbl. f. Gynäk.* 59: 2901, 1935.
12. Friedrich, B.: *Monatschr. f. Geburtsh. u. Gynäk.* 103: 211, 1936.
13. Patkay, K.: *Arch. f. Gynäk.* 169: 13, 1939.
14. Frech, H. C., Jr.: *AM. J. OBST. & GYNEC.* 33: 854, 1937.
15. Frech, H. C., Jr.: *J. M. A. Georgia* 27: 240, 1938.
16. Bowman, D. E.: *J. Biol. Chem.* 137: 293, 1941.
17. Bowman, D. E.: *J. Biol. Chem.* 141: 877, 1941.
18. Bowman, D. E.: *J. Lab. & Clin. Med.* 24: 1072, 1939.
19. Mello, M. I.: *Rev. brasil. de biol.* 2: 343, 1942.

HYPERNEPHROID CARCINOMA OF THE KIDNEY OR ADRENAL (?) AND PREGNANCY*

A. F. LASH, PH.D., M.D., CHICAGO, ILL.

(From the Department of Obstetrics and Gynecology, Michael Reese Hospital)

THE literature dealing with renal tumors as a complication of pregnancy is extremely scarce, and one may conclude that such a condition is so rare that it may be termed a clinical curiosity (Adair and Stieglitz). Stoeckel, Marz, Kneise, Braatz and Parkes have reported instances in which they removed malignant unilateral growths during pregnancy without causing abortion and with spontaneous normal outcome at term.

This group of tumors, hypernephroid carcinoma (or clear-cell adenocarcinoma) are familiar to all pathologists, but they are so peculiar in their histological characteristics and location that there is no unanimity of opinion as to their origin. They are recognized clinically by their symptoms of hematuria, pain, and tumor in the loin. But only one of these symptoms may be present at one time. Pregnancy is influenced by them only as a mechanical factor producing pressure on the kidney or ureters. The tumor may be stimulated in its malignant growth during pregnancy (Wagner).

A point I wish to make is the frequency with which the surgeon misses uterine, adnexal, and extrapelvic masses at the time of lower uterine segment cesarean section, because the operative field is restricted to the lower uterine segment. Occasionally bicornuate uteri, fibroids, and ovarian neoplasms are overlooked, and certainly extrapelvic masses are totally ignored. With proper precaution, I would suggest the careful palpation of the fundus and adnexa.

The following case report of a hypernephroid carcinoma of the kidney or suprarenal associated with pregnancy is therefore of clinical interest.

A. M., a 30-year-old white primigravida, entered the Michael Reese Hospital on June 7, 1944, because of hypertension and albuminuria with a pregnancy at term. Her prenatal observation began on Oct. 29, 1943, when she was eight weeks pregnant. At that time blood pressure was 122/80. Physical status and urinary findings were normal. During the course of her pregnancy she had transient rises of the systolic blood pressure varying from 148 to 172 but always resuming a normal level after rest, restricted diet, and elimination. She gained 18 pounds and had no pathologic urinary findings. Her past history was entirely negative.

On admission, the physical examination revealed a nervous, apprehensive individual with the findings of a full-term pregnancy. Her weight was 133 pounds. Blood pressure was 182/100. Urinalysis showed 2 plus albumin. Blood examination showed 3,860,000 erythrocytes, 5,450 leucocytes, with 85 per cent hemoglobin. Nonprotein nitrogen was 25 mg. and uric acid 4.5, per 100 c.c.

She was under a strict regime of bed rest, low-protein, salt-free diet, daily magnesium sulfate, and sedation. Since no improvement occurred and medical induction of labor failed, the interruption of pregnancy was considered.

On June 10, 1944, with the indication of a persistent pre-eclampsia, a lower uterine segment cesarean section was performed under local anesthesia, and a normal male child, weighing 3,120 grams (6 pounds, 14 ounces), was delivered. The postoperative course was uneventful and afebrile until the seventh postpartum day, when she complained of right abdominal pain, and the temperature rose to 102.4° F. with a pulse rate of 88. Her blood count showed 4,000,000 erythrocytes, 10,800 leucocytes, and 90 per cent hemoglobin. The urine contained 1 plus albumin. On physical examination a large cystic mass was found in the right upper quadrant of the abdomen with a medial tubular mass. The tentative diagnosis was torsion of a right ovarian cyst or an acute cystic degeneration of a pedunculated fibroid.

*Presented before The Chicago Gynecological Society, Oct. 20, 1944.

Two days later the blood examination showed erythrocytes 3,850,000, leucocytes 15,600, and hemoglobin 65 per cent. On repeated examination the mass remained high in the right upper quadrant and fixed, not moving with respiration. Therefore, an extrapelvic, retroperitoneal neoplasm was considered.

A consultant, Dr. M. L. Parker, a general surgeon, saw the patient on June 19, the ninth postoperative day, and his notes were:

"The exact diagnosis is not clear at this time. A high ovarian cyst is possible; a retroperitoneal tumor must also be considered. In view of the fever, relative comfort of the patient, absence of ileus, and reflex symptoms, conservative therapy is suggested."

To obtain further new information, an intravenous urography was done and reported as follows:

"A survey film followed by excretion urography revealed the following: There is a normal bilateral thrust excretion at five minutes, with progressive excretion from both kidneys at fifteen and thirty minutes. The right kidney is shown to be markedly displaced to the left, the renal pelvis actually protruding slightly to the left of the spine, crowded over by a large mass in the right lumbar region. The ureter on the right side from the ureteropelvic junction down to the sacroiliac is markedly dilated, indicating partial obstruction, probably due to pressure from the tumor mass. In the lateral view the right kidney is shown to be displaced somewhat anteriorly but the calices appear within normal limits. The left kidney appears normal throughout as to size, configuration and the renal pelvis.

"Conclusions: There is nothing characteristic about this mass to identify it except that it produces marked displacement of the right kidney. The possibility, however, of a perinephritic abscess or of a retroperitoneal tumor must be considered." (Fig. 1.)



Fig. 1.

The patient's febrile course remained the same. The blood count now was 2,970,000 erythrocytes, 10,200 leucocytes, and 50 per cent hemoglobin, so a transfusion of 500 c.c. of whole blood was given. Sulfadiazine (90 grains daily) given over five days followed by three days of penicillin (100,000 units daily) produced no change in the febrile course. Pelvic examination showed a well-involuted uterus with no pathologic findings in either the adnexa or broad ligaments. Since no change had occurred in the clinical course regardless of therapy, surgical exploration was considered desirable.

On July 15, 1944 (thirty-five days postcesarean section), with the following findings: blood pressure 112/70, erythrocytes 3,890,000, leucocytes 12,600, and hemoglobin 62 per cent,

exploratory laparotomy was undertaken by Dr. M. L. Parker. Spinal anesthesia supplemented by cyclopropane was used. With an aspirating needle, about 400 c.c. of dark, brownish-red thin fluid was obtained. A right upper abdominal incision was then made. Upon entering the peritoneal cavity, a large retroperitoneal mass was found which had pushed the ascending colon medially and superficially. The ascending colon was adherent to the mass. After freeing the colon, the parietal peritoneum over the mass was incised. The mass originated from the upper portion of the right kidney. By dull dissection the mass was freed from the surrounding areolar tissue bed and when excised from its origin the upper one-third of the kidney was separated from the lower two-thirds, requiring several mattress sutures. No other adrenal gland was observed. The peritoneum was closed and the right kidney fixed. A Penrose drain was inserted through a stab wound in the right subcostal region and the abdomen was closed in layers in the usual manner. The patient tolerated the operation well and made an uneventful recovery, going home on the fifteenth postoperative day (fifty days after her cesarean section).



Fig. 2.

The pathologic examination by Dr. Otto Saphir was reported as follows: "The specimen consists of a thick-walled saccular structure measuring 18 cm. in diameter in the collapsed state. The wall measures up to 1.5 cm. in thickness and is grayish white. The lining is ragged yellow or pink. The lumen is filled with friable spongy yellowish-red material. Microscopic examination shows hypernephroid carcinoma (clear cell adenocarcinoma) with tremendous hemorrhage and necrosis and the formation of cystlike hematomata." (Fig. 2.)

References

1. Adair, F. L., Ryerson, M. C., and Stieglitz, E. J.: *Obstetric Medicine*, Philadelphia, 1934, Lea & Febiger, p. 580.
2. Braatz, E.: *Deutsche Ztschr. f. Chir.* 48: 56, 1898.
3. Kneise, O.: *Zentralbl. f. Gynäk.* 54: 292, 1930.
4. Marz (Quoted by Schmidt, L. E.): *Surg., Gynec. & Obst.* 21: 679, 1915.
5. Parkes, C. T.: *Am. J. M. Sc.* 100: 257, 1890.
6. Stoeckel, W.: *München. med. Wehnschr.* 71: 257, 1924.
7. Wagner, G. A.: *Ztschr. f. Geburtsh. u. Gynäk.* 59: 338, 1907.

LEIOMYOMA OF THE OVARY COMPLICATING PREGNANCY

JOHN H. MOORE, M.D., GRAND FORKS, N. D.

(From the Grand Forks Clinic)

AN EXTENSIVE search of the literature has revealed only two instances of leiomyoma of the ovary complicating pregnancy. As far as is known, the present case is the third to be reported.

R. Olshausen¹ reported the case of a nullipara, aged 38 years, married for fourteen years, who came under his observation early in September, 1893. The abdomen had increased markedly in size and the patient suffered considerable discomfort, including beginning respiratory disturbances. Examination under anesthesia revealed a tumor, almost as large as a man's head, which lay half in the pelvis and half above it. The uterus lay entirely outside the true pelvis and was greatly displaced toward the right and forward. A second tumor, more irregular and more nodulated, also somewhat smaller than the one at the left, was located above the uterus and seemed to be connected with the latter. There was no ascites.

Operation was performed on Sept. 16, 1893. The tumor on the left side was lifted out of the pelvis with difficulty and had a firm pedicle, the thickness of a man's thumb. The tumor at the right had a pedicle which was attached several centimeters behind and above the right ovarian ligament. The uterus seemed to be pregnant in the third month. Both tumors were myomas, of both ovaries, but the microscopic findings were not given. One of them weighed 960 grams and the other 650 grams. Convalescence was undisturbed. On March 21, 1894, the patient gave birth to a mature living child. Manual detachment of the placenta was necessary. The puerperal period was normal.

Brachetto-Brian and Casco² reported the case of an unmarried 17-year-old girl with antecedents of dysmenorrhea and without antecedents of pregnancy who was operated upon in emergency for pelvic appendicitis. During the operation the appendix was found healthy but there was a massive intraperitoneal hemorrhage. The left ovary was removed, and its histologic study established the diagnosis of pregnancy in the cortical zone of an organ showing generalized endometriosis. The embryo was not found. No ovarian tissue was found, but it was replaced by a fibroleiomyomatous fabric. The authors concluded that the ovary in which the impregnated ovum was implanted showed a double alteration: generalized endometriosis and fibroleiomyomatosis.

Report of Case

Case No. 33867. A married white woman, 34 years of age, registered at the Grand Forks Clinic on Feb. 24, 1944. She had been married four and one-half years and this was her first pregnancy. Her last menstrual period began on Dec. 6, 1943, and her estimated date of confinement was Sept. 12, 1944. There was nothing remarkable in her antecedent history except that her previous failure to conceive had been involuntary and one year earlier she had been told, elsewhere, that she had a pelvic tumor. According to the patient, this tumor had not been found on subsequent examinations. Her chief complaints were soreness in the lower abdomen, a rapid increase in size of the lower abdomen and premenstrual sensations. Menstruation had become established at 14 years, 28-day cycle and 5 days of moderate flow.

General physical examination was not remarkable except for a soft basal systolic murmur, transmitted to the apex and, faintly, to the left axilla. Temperature was 99°F., pulse rate 100, respiratory rate 16, and blood pressure, 130/90.

There was a hard tumor on the right side of the lower abdomen, rising two-thirds of the distance to the umbilicus and moderately tender. A depression occurred in the lower mid-abdomen between this tumor and a softer mass to the left of the midline, which was comparable in size to a three months' pregnancy. The breasts were large, globular, and

engorged. The introitus was nulliparous and marital. There was a firm, hard tumor blocking the posterior cul-de-sac and a harder tumor above this and to the right. The mass in the posterior cul-de-sac could not be displaced. The cervix was high under the left pubic ramus and what appeared to be a pregnant uterus was crowded to the left side of the lower abdomen.

A soft tissue roentgenogram of the lower abdomen showed no fetal parts but increased density on the right side.

The value for hemoglobin was 72 per cent with the 17-gram Sahli tube; erythrocytes numbered 3,630,000, leucocytes, 15,200, and Kahn and Kolmer tests were negative. The sedimentation rate was 49 mm. in one hour. The differential blood count was not remarkable. The urine showed a heavy trace of sugar and the sediment showed an occasional leucocyte and erythrocyte.

She was admitted to St. Michael's Hospital in Grand Forks with a diagnosis of pelvic tumor complicating pregnancy; probably ovarian tumor. On Feb. 25, 1944, the abdomen was opened through a right lower paramedian incision. A solid tumor of the right ovary was delivered into the wound with some difficulty and a right ovariectomy was performed. There was a hard, subserous myoma on the anterior uterine wall which was showing evidence of necrosis and this was removed and the uterine wound was closed with fine plain catgut on an atraumatic needle. The abdomen was closed in layers with 00 plain and 00 chrome catgut, three silk worm tension sutures were inserted, and the skin was closed with Nylon. The anesthetic was ethylene-oxygen-ether vapor.

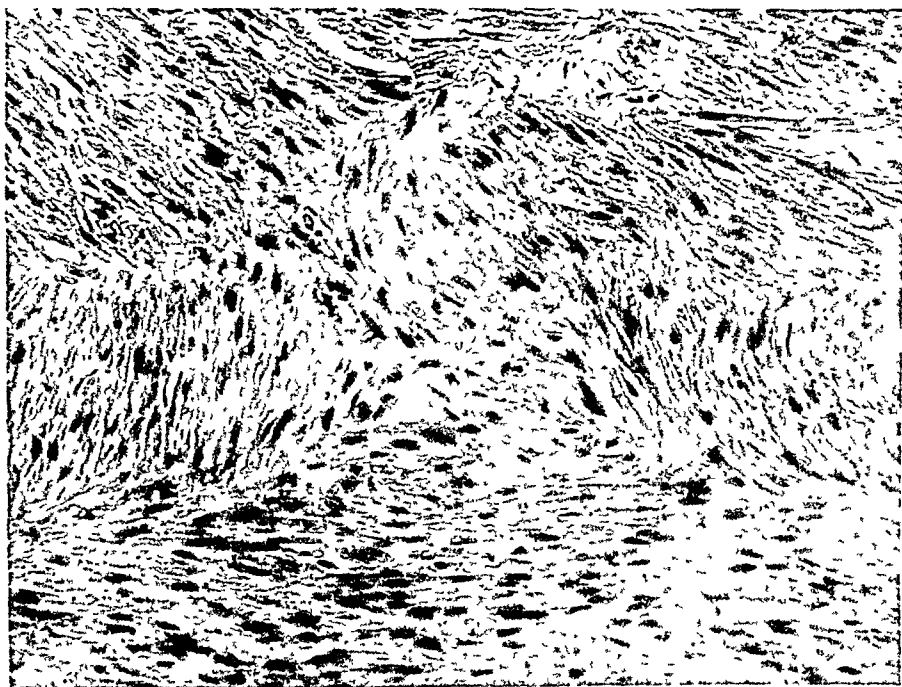


Fig. 1.

Gross Pathology.—A solid tumor of the right ovary, incarcerated in the pelvis, and weighing 1,170 grams. It measured 16 cm. in length and 13 cm. in width. Its lengthwise circumference was 43 cm. and its narrowest circumference, 31 cm. The surface was nodular but the covering was smooth and there was no evidence of implants. On section, the tumor appeared hard except for one softened area, 3 by 2 cm., near the superior surface.

The uterus was approximately the size of a three months' pregnancy and on its anterior surface was an acorn-sized subserous myoma. Several smaller "seedling" subserous myomas were present but were not disturbed. The uterus was crowded to the left of the midline and occupied the left lateral pelvic cavity, due to the pressure of the tumor in the right ovary. The left ovary was about twice the normal size and contained several follicular cysts. A corpus luteum was not positively identified. Both Fallopian tubes appeared grossly normal and were preserved. The veins of the right broad ligament were considerably engorged.

The entire specimen was fixed in formalin and sent to Dr. E. T. Bell. His report is as follows: "The ovary is entirely replaced by a massive hard tumor roughly spherical in

shape and varying in diameter from 10 centimeters to 12 centimeters. The outer surface is smooth except for a few coarse nodular elevations. On section the growth is of hard fibrous texture with no soft areas and no cysts. Microscopically the tumor is of uniform structure throughout. It is composed of adult smooth muscle with a moderate amount of collagenous tissue between the muscle fibers (Fig. 1). The diagnosis is a benign leiomyoma."

Postoperative Course.—The immediate postoperative condition of the patient was excellent, but late in the afternoon of the day of operation she began to pass blood clots from the vagina. Progestin therapy was started with the intramuscular injection of Lipolutein,* 5 mg. every four hours for the first two postoperative days, then at longer intervals until the sixteenth and final injection was given on the eighth postoperative day. There was no bleeding after the third postoperative day. Her maximum temperature was 100.6°F. on the afternoon of the day of operation. She was discharged on the fourteenth postoperative day.

Regular prepartum examinations between April 16, 1944, and Aug. 16, 1944, showed the pregnancy to be developing normally. On Sept. 1, 1944, her obstetrician, Dr. Roger H. Mattson of McVile, North Dakota, delivered her of a boy weighing 7 pounds, 8 ounces following an uneventful labor. Her postpartum course was normal.

Summary

A case of leiomyoma of the ovary complicating pregnancy is reported. A search of the literature revealed only two other cases where this type of ovarian neoplasm has been found in association with pregnancy.

References

1. Olshausen, R.: Veit's Handb. d. Gynäk. ed. 2, 1: 788, 1907.
2. Brachetto-Brian, D., and Casco, C. M.: Rev. Assoc. méd. argent. 55: 375, 1941.

*Parke, Davis & Company.

HEMINECROSIS OF CERVICAL STUMP FOLLOWING SUPRA-VAGINAL HYSTERECTOMY

ROBERT T. FRANK, A.M., M.D., NEW YORK, N. Y.

MRS. M. S., a 39-year-old nullipara, had known of the presence of uterine fibroids for seven years. She was referred to me because of increasing menstrual bleeding prolonged to from seven to nine days.

The patient was somatically normal. The genital tract was nulliparous, uninfected. The uterus was enlarged to the size of a four months' pregnancy and distorted by multiple myomas which mainly were retrocervical.

On June 8, 1942, a supravaginal hysterectomy for fibroids, right salpingo-oophorectomy for closed hematosalpinx, and appendectomy were performed. No difficulties were encountered.

The early postoperative convalescence was unusually smooth and afebrile. On the tenth day slight bleeding from the vagina was noted. On the eleventh day, profuse bleeding, chilly sensations, temperature elevation to 103.6° F. white blood count 19,000, and polynuclear count 60 per cent developed. No peritoneal symptoms existed. Sulfadiazine by mouth was prescribed.

On pelvic examination an enlargement of the portio was felt. By speculum examination a sharply demarcated necrosis of the right side of the cervix could be seen. The affected area was swollen, purple, and elevated. The process extended into the right fornix. (Fig. 1, A).

One June 21, the thirteenth day following operation, the entire necrotic area was readily removed as a slough, exposing a raw depression in the lateral fornix close to the course of the right ureter and uterine artery (Fig. 1, *B*). A packing of iodoform gauze was inserted lightly against the defect. Temperatures were from 99° to 100° F. No secondary hemorrhage developed. The patient was discharged well and fully healed on the twenty-second day. Fig. 1, *C* shows completed cicatrization as observed six months after operation. There was a minimal scar in the right fornix.

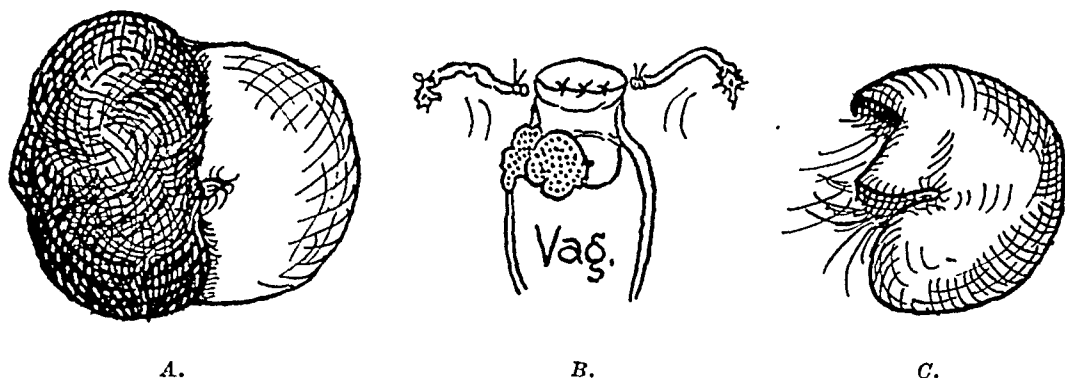


Fig. 1.—*A*, View of portio vaginalis through speculum. The right half is swollen, bluish-black in color. *B*, Diagrammatic transverse section showing extent of necrosis into right vaginal fornix. *C*, View of healed portio six months after operation. Defect and scar.

Comment.—At operation both ligatures to the uterine arteries were applied identically and at the same level. Presumably the descending vaginal vessels on the right side were anomalous and did not possess the customary free anastomosis with the ascending vaginal vessels. Consequently, the affected area (right half of the portio, right fornix) was rendered ischemic and sloughed off (dry gangrene). If the process had been due to thrombosis and infection, further extension into the fornix with secondary hemorrhage from the uterine artery might have occurred. In anticipation of such an eventuality the patient was watched incessantly and her blood typed.

A SIMPLE TECHNIQUE TO TEST TUBAL PATENCY

ALBERT DECKER, M.D., F.A.C.S., NEW YORK, N. Y.

THE production of pneumoperitoneum by the transuterine route is evidence of tubal patency. The method introduced by I. C. Rubin for testing tubal patency provides for the introduction of air or CO₂ under pressure into the abdominal cavity through the uterotubal channels. Refinements in diagnosis are provided by precise readings registered by kymographic tracings of the pressure during the insufflation. The simplest apparatus for tubal insufflation utilizes a bulb syringe, atmospheric air, and an intrauterine cannula. All methods so far used rely upon positive pressure exerted by air or CO₂, the latter being more satisfactory because of its rapid absorption time. The pressure is exerted through an intrauterine cannula while the patient is in the lithotomy position. Instances of air embolism have been reported after the insufflation of unduly high intrauterine pressures, and when air had been used for the insufflation.

Recent personal observation reveals that pneumoperitoneum can be produced by utilizing the negative intra-abdominal pressure created

by assuming the knee-chest posture. This method is safer and requires only such instruments as are usually available in the physician's office.

Technique

The patient is placed in the knee-chest posture. The perineum is elevated with a Sims speculum. The cervix is exposed, painted with merthiolate, grasped with a tenaculum, and an intrauterine cannula or metal catheter is introduced into the uterus. Because of the negative intra-abdominal pressure, an immediate pneumoperitoneum results if the tubes are patent. The amount of air entering the abdomen is usually about 150 to 300 c.c. as demonstrated by x-ray or fluoroscope. The characteristic shoulder pain and symptoms of pneumoperitoneum occur on resumption of the sitting or standing position. The negative pressure created in the abdomen by the knee-chest posture, as measured by the Zavod Aneroid Pneuro* apparatus, attains 8 to 12 c.c. of water.

Pneumoperitoneum may be produced after slight dilatation of the cervix with a cervical dilator and without introducing a cannula, with the patient in the knee-chest posture.

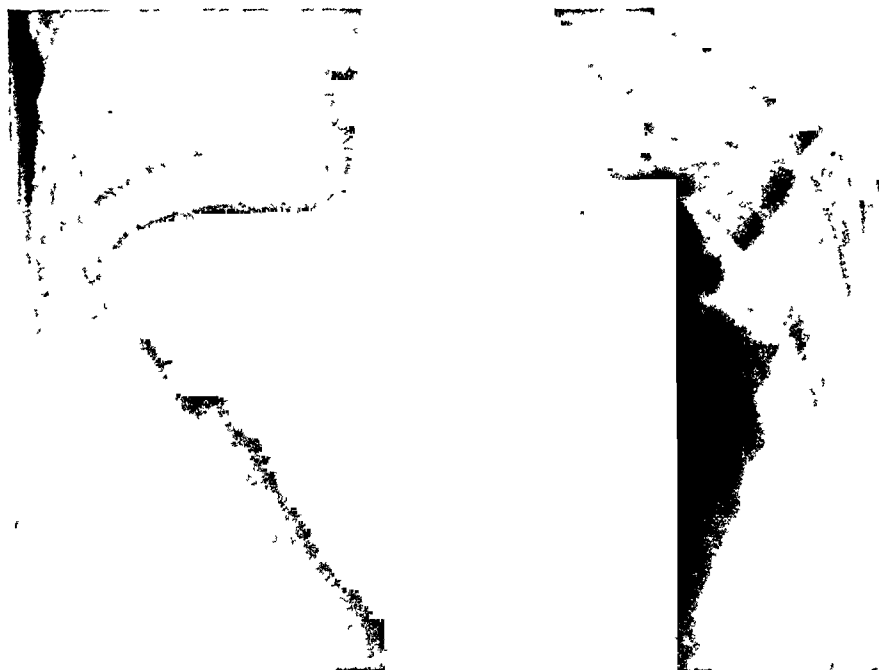


Fig. 1.

This method has several advantages; very few instruments are needed, the air enters the abdomen only if the tubes are patent, not spastic, and as a result of negative pressure created beyond the distal end of the oviduct. The pressure within the uterine cavity and tube is never elevated. The danger of air embolism is reduced. Other accidents are avoided that result from high intrauterine and intratubal pressure. When pneumoperitoneum results from the knee-chest posture, after introduction of the cervical cannula, at least one tube may be considered quite normal.

Because of the simplicity of this method, it is suggested as the initial procedure in the determination of tubal patency. A positive result will make other procedures unnecessary. This method does not allow for some diagnostic details that can only be gained by more elaborate apparatus, and it cannot be relied upon as a therapeutic measure to overcome obstruction of the oviduct. It does not offer the diagnostic detail or therapeutic effect of high intrauterine pressure, but, on the other hand, it is free from its dangers.

*Manufactured by the American Cystoscope Makers, 1241 Lafayette Avenue, Bronx, New York.

Example.—Mrs. M. J., 32 years old, white, married ten years, with one child 4 years old, had had a normal delivery. The postpartum period was prolonged (twenty-two days) because of abdominal pain, bleeding, and slight temperature.

Menstrual onset occurred at 14 years of age, was regular every twenty-eight days, duration four days. Menstruation was resumed six weeks following childbirth and has been regular since. There was no vaginal discharge.

Her weight is 130 to 134 pounds constant.

Patient has not been pregnant since birth of child four years ago, although having regular intercourse. She has never used any method of contraception. Pregnancy is now desired.

Vaginal examination was entirely negative. Because of obstetric (postpartum) history of possible infection, tubal occlusion was suspected.

The patient was placed in knee-chest posture and an intrauterine cannula was inserted through the cervix. An immediate pneumoperitoneum resulted as shown by x-ray (Fig. 1).

10 WEST 74TH STREET

Necrology

WILLIAM HANS VOGT, M.D., Professor and Director of the Department of Obstetrics and Gynecology, St. Louis University, died suddenly of heart disease at Atlantic City, New Jersey, June 17, 1945, at the age of 68, while attending as examiner a meeting of the American Board of Obstetrics and Gynecology. Born in St. Louis in 1877, he graduated from the Missouri Medical College (now Washington University), did postgraduate work in Vienna under Shauta, and Hitchman, and in Dresden under Leopold. Dr. Vogt was associated with various hospitals in St. Louis as an attending and consultant and was certified as a Diplomat of the American Board in 1932. He was a Fellow of the American College of Surgeons and a member of the American Association of Obstetricians and Gynecologists, the Central Association and Southern Medical Society, as well as a member of the Advisory Editorial Board of the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY.

Department of Reviews and Abstracts

Selected Abstracts

Menstruation, Dysmenorrhea, Etc.

Whitacre, Frank E., and Barerra, Benjamin: War Amenorrhea, *J. A. M. A.* 124: 339, 1944.

The authors report their findings among 1,172 women interned at the Santo Tomas Internment camp in Manila, Philippines. Among this group there were 125 patients with amenorrhea which had developed since the outbreak of the War. It was felt that nutritional factors had little to do with the sudden onset of this widespread condition, and that the amenorrhea observed was probably due to severe psychic shock, worry, and fear, which, acting through the autonomic nervous system, caused a complete suppression of ovarian function. Active treatment consisted of the administration of estrogenic substances, vitamin E, and reassurance.

WILLIAM BERMAN.

Hartman, Carl G.: The Normal and the Hyperactive Ovary in the Menstrual Cycle and in Hyperplasia, *West. J. Surg.* 52: 139, 1944.

Menstruation is a function limited to man, monkey, and the apes. Six types of nontraumatic bleeding must be distinguished: postpartum, abortion, placenta sign, intermenstrual, menstruation without ovulation, menstruation after ovulation. Non-ovulatory menstruation is seasonal in the monkey and is a common occurrence in women, even normal women. This menstruation is indistinguishable from that occurring following ovulation. In both cases uterine bleeding and the desquamation of tissue is the result of estrogen deprivation. Apparently the withdrawal of the estrogens is the essential factor in the induction of menstruation. Progesterone is not essential to the process.

In the monkey, long-continued pathologic bleeding practically always is associated with a small hypoplastic uterus. Bleeding, however, can be produced from a hyperplastic endometrium by a long-continued administration of the estrogens. Small doses over long periods are required, single large doses do not produce hyperplasia. Hyperestronization by endogenous estrogens from persistent follicle cysts in the monkey can produce hyperplasia with bleeding. These persistent follicles can occasionally be associated with ovulation from the opposite ovary. Normal menstruation, ovulatory or anovulatory, may occur in the presence of large follicle cysts, but the persistence of the cysts may result in complete destruction of the involved ovary. Fluid aspirated from these cysts is low in estrogen and again it is emphasized that it is long-continued stimulation of the endometrium by small doses of estrogen that brings about hyperplasia.

WILLIAM BICKERS.

Wollner, A.: The Menstrual Cycle in the Human Cervical Mucosa and Its Clinical Significance, *Am. J. Surg.* 52: 331, 1942.

The author has observed cyclic changes in the mucosa of the cervix corresponding to that of the endometrium in 70 per cent of the cases studied. He believes that the estrogenic hormone acts upon the cervix in the same way that it acts upon the endometrium. He states that he has been able to reproduce "erosions" of the cervix in menopausal women by the injection of estrogen, and that these disap-

peared when the administration of the material was discontinued. Epithelial metaplasia in the endocervix is interpreted not as evidence of a healing erosion but rather as the result of hormonal stimulation. The importance of this hormonal etiology lies in a possible relationship to the development of carcinoma.

FRANK SPIELMAN.

Gubner, Richard, and Ungerleider, Harry E.: Vitamin K Therapy in Menorrhagia, South. M. J. 37: 556, 1944.

The liver is intimately concerned with the conjugation of the estrogenic hormone for excretion. Impairment of liver function will impair the estrogen inactivating capacity and therefore permit abnormally high estrogen levels in the blood. This may produce gynecomastia, endometrial hyperplasia, premenstrual tension, and perhaps dysmenorrhea. Disturbance in liver function may also interfere with the production of prothrombin and thus retard or actually prevent the clotting of blood. The authors report on a group of patients with prolonged menstrual flow who were treated with Vitamin K for the purpose of raising their prothrombin level and thus controlling their menorrhagia by promoting clot formation. The duration of flow was reduced in approximately one-half of the patients treated.

Prothrombin studies were not carried out on all these patients. However, in two cases it was found that the prothrombin time was prolonged and the Vitamin K therapy beneficially influenced the menorrhagia in these cases.

WILLIAM BICKERS.

Nogueira, Nelson G.: Premenstrual Tension, An. brasil. de ginec. 18: 47, 1944.

The author recalls the theories of Frank (deficient renal excretion of estrogens during the days preceding menstruation causes their retention in the blood, influencing the sympathetic nervous system and producing the symptoms), of Israel (presence of nonantagonized estrogens) and of Greenhill and Freed who maintain that increase in interstitial fluids, caused by retention of the sodium ion by the ovarian steroids, is the mechanism of the various premenstrual disturbances. The increase in the tissue fluid may be slight or lead to great edema, and the symptomatology would depend on the variable fluid distribution through the involved organs. Greenhill and Freed recommended abstention from salt in the food during the last two weeks of the menstrual cycle and the daily use of 1.80 Gm. of ammonium chloride divided into three doses.

The change in the water metabolism is evident and all the factors which interfere with it must be studied carefully. They are characteristically altered in normal pregnancy and more markedly in edema associated with pregnancy. Some of these changes are also found in the menstrual cycle, and perhaps some constancy in these variations could be discovered which might explain premenstrual tension.

J. P. GREENHILL.

The Newborn

Potter, Edith L.: The Lessons to Be Learned From a Study of Infant Deaths, J. A. M. A. 124: 336, 1944.

Analysis of statistics shows that there are three principal channels into which efforts to reduce deaths in the neonatal period should be directed. These are prematurity, birth trauma, and infections. Since no one has been able to prevent the premature onset of labor, except in isolated cases, it is necessary to improve the environment into which the premature infant is born if its chances of survival are to be increased. Reduction of birth trauma can be counteracted by improved training of the obstetrician. The third principal factor is infections, and an attempt should be made to eliminate all pathogenic bacteria from the environment of the infant during delivery and after birth.

WILLIAM BERMAN.

Wessel, Morris A.: Chylothorax in a Two-Week-Old Infant With Spontaneous Recovery, *J. Pediat.* 25: 201, 1944.

Chylothorax is a relatively rare condition which may occur at any age. Most cases are believed to result from rupture of the thoracic duct itself, or from one of its tributaries, although not necessarily so.

A case of chylothorax in a 14-day-old infant is presented. The patient recovered following repeated aspiration of the right pleural cavity, for relief of recurrent respiratory difficulty. A brief review of the literature dealing with this entity is included.

JAMES P. MARR.

Halbrecht, I.: Role of Hemoagglutinins Anti-A and Anti-B in Pathogenesis of Jaundice of the Newborn (*Icterus Neonatorum Precox*), *Am. J. Dis. Child.* 68: 248, 1944.

The author found among 10,000 births only nine cases of true erythroblastosis; there was a mortality of 60 per cent.

Lenart and Biro stated that hemoagglutinins are the cause of all icterus in the postnatal period. The author is in disagreement and is convinced that agglutinins anti-A and anti-B cause only icterus precox, and not the usual physiologic icterus which does not appear until twenty-four hours after birth.

The placental blood on these newborn infants showed 1.75 mg. bilirubin content, as contrasted against 0.75 mg. in physiologic icterus and 0.55 mg. per 100 c.c. in children without icterus.

The passage of these agglutinins from the mother to the fetus by way of the placenta has been demonstrated by Hirszfeld and Zborowski and others, who showed that in 30 per cent of newborn children it is possible to find hemoagglutinins which disappear from the blood after a short time. The agglutinins anti-A and anti-B are milder hemolytic agents for the newborn than the agglutinins anti-Rh, for the former are absorbed by the antigen secreted by the tissues, while the latter is absorbed only by the red blood cells, the Rh factor being present only in the erythrocytes and not in the tissues.

Of special interest was the determination of the blood group of the infants with icterus precox and their mothers. Fifty-seven of the 60 infants, or 95 per cent, had blood incompatible with that of the mother, so that the serum of the latter agglutinated the red cells of the former. A group of 160 infants with physiologic icterus revealed that 30 per cent had blood incompatible with that of the mother, while of 2,000 infants with icterus, only 26.5 per cent showed incompatibility.

JAMES P. MARR.

Blatt, Maurice L., Zeldes, Mary, and Goodfriend, James: Epiphyseal Dysgenesis Associated With Cretinism in a Premature Infant, *Am. J. Dis. Child.* 67: 480, 1944.

In roentgenograms, epiphyseal dysgenesis is diagnosed by the appearance of multiple small irregular islets of calcification, scattered over a considerable area. The islets are irregularly spaced, and the anatomic distribution does not conform to that of the normal centers of ossification.

It is not to be confused with osteochondritis deformans, which is generally accompanied by pain and does not respond to thyroid therapy. The authors report such a case.

JAMES P. MARR.

Anderson, Nina A., Sage, Dorothy N., and Spaulding, E. H.: Oral Moniliasis in Newborn Infants, *Am. J. Dis. Child.* 67: 450, 1944.

This study was undertaken to investigate further some of the factors which may be related to the incidence, the source, and the spread of oral moniliasis in newborn infants.

Vaginal swabs were obtained from 57 of the mothers during labor, and at delivery. The occurrence of oral thrush in 6 of 13 infants whose mothers had *Monilia*

albicans in the vaginal flora is significant when compared with the incidence of oral thrush in only 4 of 38 infants from whose mothers' vaginal swabs *Monilia* was not isolated, and in only 5 of the 44 infants from whose mothers either no species of *Monilia* was obtained or only forms other than *M. albicans*.

The interval between the birth of the infant and the cultural demonstration of the presence of *M. albicans* in the infant's mouth averaged three days in those instances in which the mother had vaginal mycosis, in contrast to six and two-thirds days when the mother's vaginal swab failed to show *Monilia*.

The authors recommend that all infants whose mothers reveal a vaginitis due to *M. albicans* be isolated as a prophylactic measure. Also, that it is important to diagnose and treat all such mothers ante partum in order to reduce the possibility of the transfer of the infection to the newborn infant.

JAMES P. MARR.

Pregnancy, Physiology, Diagnosis

Landgrebe, F. W., and Samson, L.: The Hogben Pregnancy Test With a Note on the Breeding of the *Xenopus* for the Test, *J. Obst. & Gynaec. Brit. Emp.* 51: 133, 1944.

The frog test (Hogben) for pregnancy, according to the authors, is as reliable as any other test, provided at least ten days elapse since the first missed period. The authors did 258 tests for pregnancy using the Scott technique for the extraction of the urine. Two hundred and twenty have been checked against ultimate clinical findings and, except in two cases where the patient showed menopausal symptoms, were found correct. At 22° C. a result is obtained within eighteen hours and the animals require feeding and cleaning only once a week. Each toad was used over twenty-four times and still responds satisfactorily. Laboratory bred *Xenopus* can be used for the test and is capable of producing a second generation which will also respond to pregnancy urine extracts.

WILLIAM BERMAN.

Corbit, J. D.: The Effect of Pregnancy Upon Experimental Hypertension in the Rabbit, *Am. J. M. Sc.* 201: 876, 1941.

Fluctuations in the blood pressure, blood urea, and the excretion of urinary protein during pregnancy were studied in normal rabbits, and in rabbits in which arterial tension was previously raised by the experimental induction of renal ischemia. In both groups of animals it was found that pregnancy tended to produce a lowering of the systolic blood pressure a few days before the onset of labor. The return of pressure to the prepregnancy level occurred gradually during the first two to three weeks postpartum. In the normal animal there were no significant alterations of blood urea or protein-urea. In the renal ischemic animals, however, there was a slight prepartal fall of blood urea and a tendency toward the occurrence of protein urea.

The failure to produce an experimental result characterizing the features of the syndrome observed in clinical medicine is probably due to either the nature of the experimental hypertension in the animal being different from that seen in the child-bearing woman, or the physiology of pregnancy in the animal differing in those factors which account for the blood pressure changes observed in human beings.

FRANK SPIELMAN.

Craig, A. A., Lewis, F. J. W., and Woodman, D.: Survey of Vitamin C Level in Wartime in Pregnant Women, *Brit. M. J.* 1: 455, 1944.

Craig and his co-workers report some observations of forty pregnant women with respect to the degree of vitamin C saturation. This study was done under wartime conditions, which produced a lack of fresh fruit and often some deficiency of vegetables. There was a wide variation in the degree of saturation, mostly on the low side. There was also a wide seasonal variation with a definitely greater saturation from June to October.

FRED L. ADAIR.

Moll, Jorge Neval: Use of Prostigmine as Pregnancy Test and to Correct Retarded Menstruation, *Rev. de ginec. e d'obst.* 38: 177, 1944.

The author states that prostigmine acting on the parasympathetic produces vasodilatation through stabilization of acetylcholine and causes hyperemia of the endometrium. Soskin, Hechter, and Wachtel have used it for the differential diagnosis of early pregnancy and, when they found it innocuous for the pregnant uterus, have extended its use to the correction of retarded menstruation. Their results were confirmed by various Brazilian authors.

The test is positive, i.e., it releases the flow in menstrual delays depending on neurovascular changes and in lactation amenorrheas, and is negative in pregnancy and amenorrheas depending on endocrinopathies. In the latter cases, the differential diagnosis is made through biologic tests. The author presents fifteen cases which demonstrate the value of the test.

J. P. GREENHILL.

Miscellaneous

Balasquide, L. A.: Malaria in Connection With Obstetrics and Gynecology, *Bol. Asoc. méd. de Puerto Rico* 36: 269, 1944.

The author calls attention to a rare and usually misinterpreted condition caused by malaria, namely, gangrene of the external genitalia appearing in small isolated spots on the labia or assuming alarming proportions. Malaria in infancy and childhood may also cause serious delay or arrest in development of the genital organs. A marked increase in the vaginal discharge of women with chronic adnexitis has also been observed during the febrile attack. Functional disturbances of the ovary are rather frequent, but sterility seems to be out of the question, at least in Puerto Rico.

The deleterious influence of malaria on pregnancy is generally accepted. Goch found that pregnancy is interrupted in 41.3 per cent of the cases. This is a slightly higher percentage than that observed in Puerto Rico. Various factors have been incriminated for the abortion, but it is probable that it is due to a combination of these factors. Eclampsia is more frequent in women with malaria. Immunity against the disease, supposed to be conferred by pregnancy, is a myth.

An acute attack of malaria may induce labor. Although, in general, labor proceeds in a normal manner, malaria sometimes leads to uterine inertia which prolongs considerably the first stage. Many of the secondary inertias of the uterus observed in Puerto Rico are of malarial origin. The atony which occurs during labor frequently leads to severe postpartum hemorrhages.

Involution is usually retarded. Sometimes it develops so imperfectly that it constitutes another cause of postpartum hemorrhage. The lochia is more abundant and of longer duration. When attacks of malaria occur during the puerperium, lactation may disappear temporarily to reappear after the attacks, but in smaller amount.

Children born of mothers with malaria have a much higher mortality rate than those of mothers without the disease. Generally, they suffer from malnutrition, debility, defects of development, and prematurity.

Quinine is not contraindicated in the treatment of malaria of the pregnant woman, but West has demonstrated that the administration of massive doses produces auditory defects in the child. The careful use of small doses immediately after labor helps involution of the genitalia.

J. P. GREENHILL.

American Journal of Obstetrics and Gynecology

VOL. 50

SEPTEMBER, 1945

No. 3

Original Communications

THE EFFECT ON INFANT MORTALITY OF VITAMIN K ADMINISTERED DURING LABOR*

EDITH L. POTTER, M.D., PH.D., CHICAGO, ILL.

(From the Department of Obstetrics and Gynecology, the University of Chicago and the Chicago Lying-in Hospital)

WITH the discovery of vitamin K and the realization that in experimental animals spontaneous bleeding often occurred when the vitamin was absent from the diet, an interest in the possible relationship of vitamin K to bleeding in the newborn infant was immediately stimulated.

For many years hemorrhagic disease has been a subject of discussion. It was defined by Townsend in 1894 as spontaneous external or internal bleeding occurring in newborn infants, unrelated to trauma, accident, or definite disease, and this is the definition still widely used. The differences of opinion which exist concerning the incidence and mortality rates have arisen largely because of the difficulty in determining which hemorrhages are spontaneous and which are the result of some form of injury. There are no specific pathologic changes in hemorrhagic disease and the decision as to whether or not trauma is contributory to a hemorrhage seems often to be largely a matter of personal opinion.

Clifford, in a detailed discussion of hemorrhagic disease in 1939, stated that he believed the original definition should be followed, and excluded from this category "bleeding of traumatic origin in the central nervous system, liver, adrenals, etc.," but, "if the infant develops spontaneous external or internal hemorrhages in areas not directly related to the injury, the diagnosis of hemorrhagic disease is made." Likewise microscopical intracranial hemorrhage occurring in the absence of a history of trauma and associated with multiple hemorrhages in other areas was included in the classification. Using these criteria as a basis for diagnosis he concluded from the available literature that the disease occurred in from 1:118 to 1:333 births with a mortality of from 30 to 38 per cent. He found that the incidence and mortality rates both varied when the criteria demanded for the diagnosis were changed. If all types of intracranial hemorrhage were included, the mortality rose to approximately 70 per cent. If all infants with internal hemorrhage—brain, pulmonary, abdominal—were eliminated, the mortality was practically zero. Clifford in his own group of 69 cases had an incidence of 1:333 births with a 30 per cent mortality, or one death from hemorrhagic disease in every 1,000 deliveries.

*Presented before a regular meeting of the Chicago Gynecological Society, Nov. 17, 1944.

NOTE: The Editors accept no responsibility for the views and statements of authors as published in their "Original Communications."

Capon, who was among those that felt there was strong evidence that all internal hemorrhage was traumatic, stated: "In my experience gross bleeding into the suprarenal glands, the peritoneal cavity or under the capsule of the liver and spleen are generally of traumatic origin. I have not included any of these in my series although it must be admitted that any baby which has a greatly increased bleeding tendency may suffer internal hemorrhage from some slight trauma which would not affect a normal infant." He included as having hemorrhagic disease only those infants showing external hemorrhage from the gastrointestinal or urinary tracts, umbilicus, mucous membranes, or vagina, and was careful to exclude any with a history of trauma, asphyxia, sepsis, or syphilis. The incidence of hemorrhagic disease according to his conception was 1:520 with a mortality of 10.8 per cent, or one death from hemorrhagic disease in every 5,000 deliveries.

Rodda, on the other hand, was particularly impressed by cerebral hemorrhage as a manifestation of hemorrhagic disease and believed that it was frequently due to mild trauma accompanied by delayed coagulation and prolonged bleeding time. He gave figures from various small series of autopsies in which the incidence of intracranial hemorrhage as a cause of death ranged as high as 76 per cent, and stated that he himself believed these figures did not exaggerate the importance of intracranial hemorrhage as a cause of death, and that the majority of such hemorrhages could be prevented if the coagulation time of all newborn infants was determined and whole blood was given intramuscularly as a prophylactic procedure when the coagulation time was prolonged.

Following the publication of Rodda's paper in 1920, the question as to whether a prolongation of coagulation time is an essential feature of hemorrhagic disease has been repeatedly raised. Clifford, in 1939, stated that if only those cases where a prolongation could be demonstrated were included, hemorrhagic disease would be a rare condition of little importance. Sanford and Leslie, on the other hand, demanded a prolongation before making such a diagnosis, and in 1938 reported finding only two cases of true hemorrhagic disease among 5,500 newborn infants, an incidence of 1:2,750.

The discovery of vitamin K, the establishment of adequate methods of determining prothrombin levels, and the recognition that the vitamin is related to the amount of prothrombin in the blood gave a new impetus to the study of hemorrhagic disease.

Numerous investigators have shown that the prothrombin time is prolonged beyond the normal adult average in practically all infants from the second to the fifth day of life. Some, Javert and Moore, Snelling and Nelson, Hellman and Shettles, Brinkhous, Smith, and Warner have reported a prolonged prothrombin time in cord blood; but others, Webster and Fitzgerald, Richdorf and Kearney, Russell and Page, Valentine et al., Waddell and Guerry, Quick and Grossman, Nygaard, Owen et al. have found prothrombin time within the normal adult range at birth, with the prolongation starting toward the end of the first day and returning to relatively normal limits by the end of the first week. Fitzgerald and Webster stated that, although the prothrombin in cord blood may be low, other unknown substances cause cord blood to coagulate more rapidly than normal adult blood. Infants vary in the degree of prolongation, and there is no unanimity of opinion concerning the limit of physiologic prolongation and the beginning of a pathologic state. Although 30 per cent of normal is accepted by most investigators as definitely pathologic, many babies with levels considerably lower show no evidence of hemorrhage. The evidence (Hellman and Shettles, Kato and Poncher) suggests that premature infants are more subject to abnormalities of prothrombin time than are infants at term, but this has not been definitely proved. According to Webster and Fitzgerald the administration of barbiturates to the mother during labor causes an excessive prolongation of prothrombin time, but Hardwicke was unable to confirm this.

It has been shown that vitamin K has a definite effect in reducing the coagulation time when the prolongation is due to prothrombin deficiency. By giving vitamin K to infants immediately after birth, or by administering it to the mother within the twenty-four-hour period prior to delivery, this drop in prothrombin can be prevented.

Investigators have varied greatly in their recommendations concerning the dosage and preferable time of administration of vitamin K. Lawson recommended giving vitamin K daily to all pregnant women for one month prior to the expected date of delivery, and Valentine et al. attempted this form of administration although many of their mothers actually received the drug for much shorter periods. Mathews stated that it should be given all women for two weeks prior to delivery, that it should be continued for the first six days after delivery if the infant is breast fed, and that, in addition, the babies themselves should receive vitamin K in one large dose intramuscularly at birth or in small doses orally for six days. According to Hellman and Shettles it should be given daily for at least two weeks before delivery. Dam agreed on a two-week period of administration but thought it essential to give the last dose within two to twenty-four hours of delivery. Fiechter believed five to ten days of administration prior to labor was necessary to give normal levels. Snelling and Nelson at one time thought it advantageous to give vitamin K daily one or two days prior to delivery but subsequently concluded that one dose given after the onset of labor and two or more hours prior to delivery was sufficient. Poncher stated that since there is no evidence of a cumulative effect, giving it for more than one week prior to delivery was useless, and that adequate results could be obtained by giving a single dose at the onset of labor.

Many other investigators have concluded that one dose given to the mother during labor was sufficient to prevent a prolongation of the infant's prothrombin time. One of the largest series to show the effectiveness of a single dose was that of Webster and Fitzgerald. In agreement are Huber and Shrader, Mull et al., Beek et al., Bohlender et al., McReady et al., and Parks and Sweet. Fitzgerald and Webster found it effective when administered orally from forty-five minutes to twenty-six hours prior to delivery, or parenterally as late as fifteen minutes before delivery. McReady et al. believed the interval between administration and delivery should not exceed fifteen hours, Mull et al. tried to give it four to ten hours before delivery, Clifford thought there should be an interval of at least three hours, Huber and Shrader of at least two hours, while Bohlender et al. could find no difference in the effect when the interval range was from five minutes to twenty-four hours.

Although Shettles, Delfs, and Hellman thought they obtained a more uniform shortening in the prothrombin time of cord blood by maternal administration, and the comment has been made that intracranial and other forms of hemorrhage could more probably be prevented by giving the drug to the mother than to the infant, many investigators believe equal protection can be afforded by giving the vitamin to the mother or to the infant itself (Bruchsaler, Toohey, Fitzgerald and Webster), that if the mother had not received the vitamin it could be given the infant after birth (Huber and Shrader), while only a few have felt that administration to the infant itself was preferable (Richdorf and Kearney, Sanford et al.). Warner has reported that the amount of vitamin K required is so small as to be easily satisfied by prelacteal feedings of cow's milk, and Salomonsen and Nygaard, and Gellis and Lyon have been of much the same opinion. Russell and Page thought a 1 per cent vitamin K ointment rubbed into the skin gave adequate protection. Vollmer et al., on the other hand, stated that every infant should receive vitamin K (preferably through the skin) regardless of whether it had been given to the mother, and Waddell and Lawson reported that on their service the antenatal administration of the vitamin to the mother before labor was supplemented by giving it to the infant during the first few days of life. Clifford, too, stated: "To provide every possible protection in the light of our present knowledge and experience, every newborn baby could well be given vitamin K at birth whether or not there has been previous maternal administration."

After studying the work of many investigators it seems reasonable to conclude that the usual prolongation of prothrombin time in the blood of the newborn can ordinarily be prevented by giving a single dose of vitamin K to the mother during labor or to the infant after birth.

Although Fitzgerald and Webster, and Sanford et al. have shown a slight elevation of prothrombin in the blood of the mothers who received vitamin K, no appreciable maternal effect is to be expected from such medication. Portes and Varangot reported finding the longest prothrombin times in the mothers of the infants who showed the greatest prolongation, but most investigators have failed to find any correlation, and regardless of the degree of prolongation of the infant's prothrombin time, that of the mother has never been shown to be outside of the normal range.

The demonstration that prothrombin time is prolonged in many infants gave rise to the particular investigation of prothrombin time in hemorrhagic disease of the newborn infant. Although previous investigators had not been of the uniform opinion that the coagulation time was necessarily prolonged in hemorrhagic disease, new reports seemed to indicate that all infants on whom such a diagnosis was made had a prolonged prothrombin time, that this was shortened by the administration of vitamin K, and that the disease was cured. Since vitamin K given to the mother or infant would prevent prolongation of prothrombin time, and since the prevention of prolongation of prothrombin time was believed to mean prevention of hemorrhagic disease, a great many investigators (Ballou, Beck et al., Bohlender et al., Bruchsalter, Clifford, Dam, Fiechter, Hellman and Shettles, Huber and Shrader, McReady et al., Valentine et al., Webster and Fitzgerald) have recommended the routine prophylactic administration of vitamin K to all women during labor, and many have made amazing statements concerning the decrease in infant mortality which could thus be brought about.

Waddell and Lawson stated: "Every infant born at the University of Virginia Hospital is treated with vitamin K through the mother and this treatment is supplemented by oral administration of vitamin K in the first few days of life. Our experience convinces us that hypoprothrombinemia and associated neonatal hemorrhage will not occur in infants so treated and that so-called traumatic birth injury has been and will continue to be materially lessened." Mull et al. reported that "administration of the synthetic vitamin K to women in labor has been adopted as a routine procedure at the Maternity Hospital and the Cleveland City Hospital." Mathews believed that "routine use . . . will turn hemorrhagic disease into a thing of the past and will drop to nil this occurrence of babies normal at birth becoming idiots due to hemorrhagic disease in the first week." Kato and Poncher said: "While in some cases of intracranial hemorrhage birth trauma was the precipitating factor, the severity of the bleeding was apparently induced by a lowering of prothrombin level of the infant's blood. Since it is not possible by antepartum examination of the maternal blood to detect which infants will have a prothrombin deficiency the administration of vitamin K to the mother shortly before delivery is suggested." Javert was a little more conservative and suggested that "the prophylactic use of vitamin K therapy in mothers and their infants with prolonged labors, short severe labors, toxemia of pregnancy, and treated syphilis may lower the incidence of hemorrhagic disease and (non-traumatic) intracranial hemorrhage."

Sage startled his readers by the statement: "Vitamin K may well prove to be a life saver for 30,000 to 80,000 American babies annually." This seems a little optimistic in view of the fact that in the United States in 1940 only 67,866 babies died under one month of age. Lehmann, using the decrease in incidence of fatal intracranial hemorrhage in a group of infants receiving vitamin K after birth as compared to a similar group receiving none, concluded that the routine use of vitamin K should cause a decrease in mortality of 1.6 per 1,000 births, making a saving of 160 babies in the 100,000 born annually in Sweden.

Writing for a nonmedical audience Richardson stated: "It is fair to believe that the general use of this latest of the vitamins will be the cause of great reduction in our infant mortality. . . . The life-saving function of the newly discovered vitamin K has been widely publicized in the scientific journals and the medical colleges and its use has been adopted by all up-to-date obstetricians and pediatricians. . . . If all expectant mothers were given vitamin K for a month before delivery and all babies were given a single dose of it immediately after their arrival, bleeding at birth would be reduced to a minimum—to those so badly injured that nothing can save them. This goal is indeed an inspiring one and the rank and file of American doctors can be trusted to attain it."

The evidence that vitamin K will prevent a prolongation of prothrombin time and will bring back to normal one that is already prolonged appears conclusive. This is the only claim that is made for it by the proponents of routine antenatal or neonatal administration. In order to determine whether routine administration to all patients is desirable, it becomes extremely important to

attempt to determine the incidence and mortality rate of hemorrhagic disease and of the number of hemorrhages that result in disability or death which are due to prothrombin deficiency.

Beck et al. gave 2 per cent as the incidence of hemorrhagic disease. According to Dam, "The percentage of babies with actual bleeding in the first week is about one per cent." Roberts stated that 0.7 per cent of the 19,052 infants in this series suffered from intracranial hemorrhage but considered this figure probably too low due to inadequacy of the data. Hellman et al. reported an incidence of 1:200 cases and included "hemorrhages, minute in brain, lungs, spleen, adrenal, thymus and liver," as well as cerebral hemorrhage, subcapsular hematomas of the liver, etc. Interestingly enough, in spite of the fact that the incidence of hemorrhagic disease was stated to be 0.5 per cent, Hellman believed he had reduced mortality from 4 per cent to 1.5 per cent, or five times the incidence of hemorrhagic disease, by giving vitamin K to prevent this condition. Waddell also reported 0.5 per cent and this figure is frequently quoted by other authors as the incidence of hemorrhagic disease.

In marked contrast to these figures is Sanford's statement that hemorrhagic disease, due to prolonged coagulation time, was found only twice among 5,500 babies.

Recent studies of infant mortality from several large obstetric hospitals give interesting figures. D'Esopo and Marchetti, at the Sloane Hospital for Women and the New York Lying-In Hospital, reported 21 fatal cases of hemorrhagic disease in 25,823 deliveries; Tyson at the Philadelphia Lying-in Hospital found hemorrhagic disease diagnosed as the cause of death in 8 of 15,488 deliveries. Clifford at the Boston Lying-In Hospital stated that fatal hemorrhagic disease occurred in 0.06 per cent of 31,786 deliveries, which would be about 19 cases. Potter from the Chicago Lying-in Hospital reported only 4 deaths due to hemorrhagic disease in 27,321 deliveries. This makes a total of 52 cases of fatal hemorrhagic disease in 100,378 deliveries, an incidence of approximately one in 2,000.

From the early papers following the discovery of vitamin K, it seemed that all infants with hemorrhagic disease suffered from prolonged prothrombin time, that this returned to normal following administration of vitamin K, and that the bleeding immediately ceased. Waddell and Guerry reported seven of eight infants with hemorrhagic disease cured by vitamin K, Kato and Poncher reported a cure in all of 22 cases, and Kato makes the statement: "Before the advent of specific therapy the mortality from hemorrhagic disease of the newborn has been estimated to have varied from 30 to 50 per cent; with the institution of vitamin K treatment the condition now need not be fatal." Waddell by personal contact with various investigators collected records of 4,141 infants treated with vitamin K prophylactically in which no case of hemorrhagic disease occurred.

Only a few investigators have questioned the efficacy of vitamin K in stopping or preventing hemorrhage. Parmalee has reported two cases of severe melena associated with marked prolongation of prothrombin time, in which the bleeding did not stop following vitamin K administration in spite of the fact that the prothrombin time returned to normal very promptly. Scobbie failed to find the prothrombin time prolonged in all of 15 cases of hemorrhagic disease in which it was determined, and stressed the fact that many infants without hemorrhage exhibited prothrombin times as prolonged as those with severe hemorrhage.

Ponches stated: "Vitamin K prophylaxis with the correction of the hypoprothrombinemic state is only one phase in the management of hemorrhage in the newborn period and is not a substitute for good obstetrical care and the prevention or prompt recognition and treatment of the other factors." Kove and Siegel, Capon, Snelling, and other investigators have commented that some additional factor is necessary before a prolonged prothrombin time will produce hemorrhage.

When Sanford and his co-workers published their study of vitamin K in relation to the occurrence of hemorrhage, their conclusion that the administration of vitamin K had not modified the incidence of hemorrhagic manifestations was met with a storm of comment. They reported an equal incidence of gastrointestinal, vaginal, umbilical, dermal, cerebral, and subepicranial hemorrhages in a group of 711 newborn infants given vitamin K by mouth immediately after birth, and in 782 who were not given the vitamin. The mortality was the same in the two groups. They felt that conditions other than vitamin K deficiency were probably responsible for the majority of hemorrhagic manifestations in the newborn infant, and that infants should not be included in the category of hemorrhagic disease simply because they had some evidence of bleeding.

They state: "In the reports of hemorrhagic disease during the newborn period that have been published recently it is apparent that all of these hemorrhagic manifestations have

been lumped into the one term "hemorrhagic disease of the newborn), which, it is assumed, is due to a deficiency of prothrombin. We have been unable to show that these hemorrhagic manifestations were associated with a prothrombin deficiency, nor were they lessened by the administration of vitamin K." They believed no baby in their series had hemorrhagic disease, and although they showed definitely that administration of vitamin K will shorten the prothrombin time and is consequently of value in the treatment of any condition due to a prolongation, they concluded that, except in true hemorrhagic disease, administration of the vitamin is without value. The incidence of hemorrhagic disease in their experience was 1:2,500 births.

Immediately after the publication of this article, Quick, in a communication to the *Journal of the American Medical Association*, said: "If the aim of Dr. Sanford and his associates is to emphasize that hemorrhages in the newborn can occur from causes other than prothrombin deficiency, they are serving a laudable purpose; but on the other hand if they are attempting to depreciate the value of vitamin K in preventing and curing the hemorrhagic disease of the newborn, one is forced for the sake of the newborn baby to take sharp issue with them."

It would appear that Dr. Sanford had not been depreciating the value of vitamin K in the treatment of hemorrhagic disease, but had been definitely questioning whether the incidence of true hemorrhagic disease was sufficient to warrant the administration of the drug to very large numbers of patients in order to prevent the disease in a very few.

A few weeks later Waddell, also in a communication to the *Journal of the American Medical Association*, stated that he was "forced to join with Dr. Quick in taking prompt and sharp exception to Dr. Sanford's conclusions." He quotes the work of Beck et al., and Hellman et al., giving conclusive proof that mortality rates can be greatly decreased and the incidence of hemorrhage reduced by the prophylactic administration of vitamin K to the mother prior to delivery, and adds, somewhat ambiguously, "we have also repeatedly expressed the hope, adequately supported by facts, that infant mortality resulting from intracranial hemorrhage will in the future possibly be materially reduced by this sound therapeutic procedure." Among his own patients he gives the amazingly high incidence of 10.4 per cent with hemorrhage in a control group of infants and 1.07 per cent in another group, the difference supposedly being due to the use of vitamin K.

Kugelmass, also commenting on Sanford's paper, stated that hemorrhagic disease of the newborn is a disease entity due specifically to prothrombin deficiency and that "since the disease occurs in less than 0.5 per cent of all newborn infants it is folly to waste vitamin K on 99.5 per cent of the remainder even if many of these may show hemorrhagic manifestations! If the latent hemorrhagic tendency present in all newborn infants becomes active, the rise in clotting time will indicate decrease in available prothrombin. Then, and only then is vitamin K therapy indicated." His incidence of hemorrhagic disease is 12.5 times that given by Sanford but there is no comment as to the source of the data, and in spite of this greater frequency he still does not believe routine administration of vitamin K justified.

According to Dam, Sanford's view "is in fact difficult to understand since sufficiently lowered prothrombin time always will lead to bleeding." Dam's statement, however, does not reflect the general opinion of most investigators.

An editorial in the English publication, *Lancet*, commended Sanford's paper for throwing scientific doubt "on what was becoming too simple—low prothrombin, hemorrhagic disease, vitamin K, cure," and concluded that "it is palpably absurd to lump all hemorrhagic manifestations of the newborn together and pretend that this is hemorrhagic disease due to prothrombin deficiency and preventable and curable by giving vitamin K."

After reading the editorial on Sanford's paper, Capon agreed that the paper gave welcome support against the idea of many recent investigators that hemorrhagic disease includes all types of hemorrhage, and said, "There is some additional factor with low prothrombin of the blood causing hemorrhagic disease of the newborn infant."

MacPherson and Henderson, in response to the same editorial, thought that one could relegate to the "proper station such minor accidents as Sanford describes" but that this still did not depreciate the routine use of vitamin K as a preventive or cure of hemorrhagic disease.

Parks and Sweet, in an attempt to find further evidence as to the validity of the statement that vitamin K could be expected to reduce materially the number of infants with hemorrhage and to decrease total death rates, gave 5 mg. vitamin K orally on admission to the hospital to 1,151 women, alternating them with 1,594 who received no vitamin K. They found abnormal bleeding in 1.7 per cent of the infants born to the first group of mothers

and in 1.4 per cent of the second group. The mortality among infants weighing over 1,000 grams alive on admission and dying within two weeks, whose mothers received vitamin K, was 4.1 per cent; for those whose mothers were untreated, 4.9 per cent. Hemorrhage not definitely due to trauma was associated with 10 per cent of deaths in both groups. The vitamin K was effective in raising the blood prothrombin levels of both mothers and infants. They say, "If an elevated prothrombin level is a significant factor in preventing neonatal hemorrhage we are unable to explain the results of our clinical survey." This paper, although appearing at about the same time as the one by Sanford et al. and in fundamental agreement with it, seems to have received little attention.

It is the paper of Beck and his co-workers and the work of Hellman and his associates that are most constantly referred to as giving proof of the efficacy of vitamin K in materially lowering the incidence of hemorrhage, and consequently in lowering infant death rates.

Beck et al. alternated cases and gave vitamin K to 1,022 mothers; among their infants 4 appeared to have suffered intracranial hemorrhage, one had bloody stools. The mothers of 1,037 infants received no vitamin K; in this group there were 14 infants with a diagnosis of intracranial hemorrhage and 7 with bloody stools. This is an apparent reduction in the incidence of hemorrhage from 2 to 0.5 per cent. There is no mention of how the diagnosis of intracranial hemorrhage was made nor of the mortality rate, and Beck, in closing the discussion on the paper, stated in regard to the infants with bloody stools, "These were not typical cases of melena neonatorum but in all of them a diagnosis of bleeding of some character was made." The incidence of 2 per cent with hemorrhage which was found in the control series is much higher than that reported by almost any other clinic.

Hellman, Shettles, and Eastman, in 1940, reported a mortality of 4.1 per cent among the infants of 384 women who had had vitamin K prior to delivery and only 1.5 per cent among 392 without vitamin K. They state that this is a statistically significant difference, and yet it is not a sufficiently large series on which to base an opinion, for it is the experience of practically every clinic delivering large numbers of babies that many hundreds may be born with almost no mortality, only to be followed by a compensatory increase a short time later.

Realizing this fact, Hellman and Shettles subsequently reported over 1,000 infants whose mothers had had vitamin K and approximately an equal number whose mothers had not been given the vitamin. The incidence of prematurity was almost twice as great and of cesarean section almost four times as great in the control as in the treated cases. The uncorrected mortality was given as 3.9 per cent and 1.9 per cent and the statement was made that, since the mortality following cesarean section was 12 per cent in each series, the variation in the number in the two series can be disregarded. However, the difference between 12 per cent of 100 cesarean sections and 12 per cent of 26 cesarean sections immediately weights the untreated series by adding 9 deaths to that group. The authors stated that, in removing all deaths of preautres or following cesarean sections, the mortality was 1.2 in the treated and 2.4 in the untreated. If the figures are recalculated, however, it seems probable that only the premature infants were removed. If cesarean sections are also eliminated, the mortality becomes 0.9 in the treated and 1.5 in the untreated, a difference less impressive than between 3.9 and 1.9 per cent. In small groups of 1,000 cases each, a difference between 9 deaths and 15 deaths can be due to chance.

In order to further evaluate the claims made by various investigators that vitamin K if administered to all pregnant women during labor would reduce neonatal mortality rates by decreasing the number of infants who die of hemorrhage, a study of this subject was initiated at the Chicago Lying-in Hospital. Most previous investigations have included a very small group of patients or the vitamin has been given to alternate women. In order to overcome the inaccuracies inherent in inadequate data, and the selection which is inevitable when an attempt is made to alternate patients, it was decided to give vitamin K to all women delivered during a two-year period, to stop this medication and to use the following two years for a control. The vitamin in the form of 3.2 mg. Hykinone (2-methyl-1, 4-naphthohydroquinone-3-sodium sulfonate)* was given

*The author is grateful to the Abbott Laboratories for supplying the Hykinone used in this entire study.

to all patients on admission to the labor rooms. The parenteral route was chosen in order to prevent loss by emesis.

Personal Observations

From Jan. 1, 1941, until Nov. 1, 1944, 13,190 infants weighing over 1,000 grams were born in this hospital. Among 6,502 mothers delivered during the first two years, 6,004 received vitamin K. The reasons for failure to administer it to 498 included too short an interval between admission and delivery, antepartum death of the fetus, nonavailability of the vitamin. Of the 6,004 patients who received vitamin K, the exact interval between the administration of K and delivery was recorded in 5,833. Almost half of the patients (45.53 per cent) received it more than one but less than six hours prior to delivery. In 7.46 per cent the interval was less than one hour; it was more than six and less than twelve in 25.04 per cent; from twelve to eighteen in 11.3 per cent; eighteen to twenty-four in 6.0 per cent and over twenty-four in 4.6 per cent.

A total of 6,560 infants were born; of these 89 died within ten days of birth, and 108 were dead at the time of delivery. This is a neonatal mortality of 13.4 per 1,000 births and a stillbirth rate of 16.4, making a total fetal and infant mortality of 29.8 per thousand births.

On Jan. 1, 1943, the administration of the vitamin was discontinued, and from then until Nov. 1, 1944, a total of 6,630 infants were delivered. Among these, 82 were stillborn and 90 who were born alive failed to survive for ten days. This gives a neonatal mortality rate of 13.5 and a stillbirth rate of 12.3 or a combined rate of 25.8 per 1,000 births.

During 1941 and 1942, the vitamin was given to a few babies after birth whose mothers had failed to receive it during labor. During the following two years it was also occasionally administered, particularly to very premature babies, but fewer than 100 received it. It was given empirically because of the possibility that it might increase the chances of survival, and only rarely because of visible bleeding.

Examination of the death rates for the two years during which vitamin K was given and for the following two years show almost identical rates for the first ten days of life, and a distinctly lower stillbirth rate in the control series. It might be argued that other more favorable conditions existed during 1943-1944 which offset any loss of life occasioned by the failure to administer vitamin K. During the latter years the proportion of multiparous patients was slightly greater than in the previous years but, as shown in Table I, the total mortality rates decreased in both multiparous and primiparous patients and in both years the rate for multiparous is greater than for primiparas. If the rates for 1943-1944 were to show any change because of the increase in the number of multiparas, it should be in the direction of increased mortality.

The incidence of prematurity (weight from 1,000 to 2,500 grams) among liveborn infants is slightly less (Table II) in 1943-1944 (6.5 per cent) than in the previous years (7.1 per cent) but the difference is only 0.6 per cent and is not statistically significant. The premature mortality rate is 12 per cent in both periods. Mortality for infants born alive at term (over 2,500 grams) is 0.5 per cent in both periods.

The incidence of various methods of delivery shows little variation in 1941-1942 and 1943-1944 (Table III). Low and outlet forceps were used slightly more frequently during 1943-1944 and natural cephalic deliveries were com-

TABLE I. MORTALITY RATES IN RELATION TO MATERNAL PARITY

	TOTAL BIRTHS	DEATHS		STILLBIRTHS		DEATHS AND STILLBIRTHS PER 1,000 BIRTHS
		NUMBER	PER 1,000 BIRTHS	NUMBER	PER 1,000 BIRTHS	
1941-1942 (Vitamin K)						
Primiparas	3,130	36	11	56	17	28
Multiparas	3,430	53	15	52	15	30
1943-1944 (No Vitamin K)						
Primiparas	2,692	34	13	30	11	24
Multiparas	3,938	55	13	52	13	26

TABLE II. RELATION OF PREMATURITY TO MORTALITY

	BIRTHS		DEATHS		STILLBIRTHS	
	(NO.)	(%)	(NO.)	(%)	(NO.)	(%)
<i>1941-1942 Vitamin K</i>						
Term	6,092	92.9	31	0.5	53	0.9
Premature	468	7.1	58	12.4	55	11.7
Total	6,560	100.0	89	1.3	108	1.6
<i>1943-1944 No Vitamin K</i>						
Term	6,198	93.5	34	0.5	43	0.7
Premature	432	6.5	56	12.9	39	9.0
Total	6,630	100.0	90	1.3	82	1.2

TABLE III. METHOD OF DELIVERY IN VITAMIN K AND CONTROL SERIES

	VITAMIN K 1941-1942	NO VITAMIN K 1943-1944
Total infants	6,560	6,630
Natural cephalic	50.7%	44.7%
Low forceps	37.2	43.3
Midforceps	2.9	2.6
Version and extraction	0.7	0.6
Breech	4.1	4.1
Cesarean	4.0	4.4
Other	0.4	0.3
Total	100.0%	100.0%

pensatorily decreased. Although total mortality is somewhat greater in natural cephalic deliveries than when low forceps are used, this is because the majority of macerated and malformed fetuses are delivered without operative interference. When fetuses dead before the onset of labor and those suffering from malformations or erythroblastosis are deleted, the mortality rates associated with the two types of delivery are practically identical. It is evident, therefore, that manner of delivery has not affected mortality rates in these two periods.

Of the 369 infants who were born dead or died during the four years, 334 were subjected to postmortem examination. The causes of death are shown in Tables IV and V. The pathologic lesions found in the infants who were born alive show remarkable similarity in the period when vitamin K was given and when it was discontinued. Each group has approximately the same number of infants with hemorrhagic manifestations, and associated with practically all of these there were abnormalities of labor or delivery which appeared to be definite causative factors. Placenta previa, premature detachment of the placenta, or cord prolapse were the cause of the anoxia which caused petechial hemorrhages in eleven infants, and were also present in the majority of infants with pulmonary hemorrhage. Intracranial hemorrhage was almost always associated with definite trauma incurred during labor or delivery.

TABLE IV. STILLBIRTHS IN VITAMIN K AND CONTROL SERIES

	VITAMIN K 1941-1942	NO VITAMIN K 1943-1944
Total births	6,560	6,630
Malformation	13	6
Erythroblastosis	6	9
Pneumonia	7	0
Syphilis	1	1
Abdominal pregnancy	2	0
No abnormalities	48	36
Antepartum		
Toxemia	11	6
Nontoxic	35	27
Intrapartum		
Nontoxic	2	3
	77	52
Anoxia (petechial hemorrhages)	27	26
abruptio	8	13
cord prolapse or knot	11	6
uterine abnormality	4	4
placenta previa	4	3
Intracranial hemorrhage	4	3
Liver hemorrhage	0	1
	31	30
Total	108	82
Stillbirth rate per 1,000 births	16.4	12.3

TABLE V. NEONATAL DEATHS IN THE VITAMIN K AND CONTROL SERIES

	VITAMIN K 1941-1942	NO VITAMIN K 1943-1944
Total births	6,560	6,630
Prematurity (no abnormalities)	27	26
Malformation	18	23
Erythroblastosis	7	12
Pneumonia	12	7
Edema of meninges	4	2
Miscellaneous	2	2
Unknown	1	3
	71	75
Anoxia (petechial hemorrhages)	6	5
Intracranial hemorrhage	9	5
Pulmonary hemorrhage	2	5
Hemorrhagic disease (?)	1	1
	18	16
Total	89	91
Death rate per 1,000 births	13.5	13.5

In only two infants did the possibility of true hemorrhagic disease exist, and in neither of these is the diagnosis conclusive. One 3,100-gram male infant, the child of a 22-year-old primigravida, was delivered naturally from a cephalic position after a labor of 7 hours and 13 minutes. Hykinone (3.2 mg.) was given 2 hours and 10 minutes before delivery. Heart tones had been irregular during the latter part of labor and meconium was evacuated into the amniotic fluid. Respiration was delayed for several minutes after birth and when finally initiated remained irregular and grunting in character. The infant was placed in a Hess bed, given oxygen and respiratory stimulants, but continued to do poorly and died after 29 hours and 30 minutes. Autopsy examination disclosed multiple perforations of the stomach with a large amount of blood in the stomach and in the peritoneal cavity, a small hemorrhage in the right adrenal gland, and early pneumonia, together with large numbers of epithelial cells from the amniotic fluid in the pulmonary alveoli.

The second infant was born in June, 1944. It was a female, weighed 3,795 grams, and was delivered by low forceps after an uneventful labor of 15 hours, 10 minutes. The mother

was a 24-year-old primipara. Respiration was extremely delayed and intratracheal oxygen was given for twenty minutes before breathing began. The infant was placed in a Hess bed and continued to do poorly. It was cyanotic, breathed irregularly, and did not move unless stimulated. It was given 3.2 mg. Hykinone one hour after birth, together with coramine and caffeine. At 6 hours of age it vomited a small amount of blood and had bloody stools; a second dose of vitamin K was given at this time. The infant continued to do poorly, and 60 c.c. of blood were given intravenously at 18 hours. There was little response and the infant succumbed at the age of 50 hours. Autopsy examination revealed a spectacular picture of hemorrhage and infarction of liver, spleen, kidneys, lungs, and adrenal glands. There was also free blood in the intestine. The brain and cranial cavity were normal. Blood smears made on the first day of life showed no evidence of platelets, and subsequently it was learned that the mother of the infant was very subject to skin petechiæ, that her maternal grandfather was a "bleeder," that a maternal aunt died at 18 months of multiple hemorrhages, and that her mother had an unusual tendency to bleed. Whether this should be considered hemorrhagic disease, whether it is entirely the result of anoxia, or whether it is some type of familial purpura cannot be determined.

If these are cases of hemorrhagic disease, they are instances of a failure to respond to vitamin K. If they are not hemorrhagic disease, it means that, in over 13,000 infants, none has died of hemorrhagic disease.

The stillbirth rate was 4 per thousand less during 1943-1944 than during the time when vitamin K was given. This saving has been almost entirely in deaths which could in no way be related to prothrombin time. The incidence of any type of hemorrhage is practically the same in the two groups, and in these, as in the neonatal deaths, there is no evidence that anything beyond trauma or interference with oxygenation of the fetal blood was a causative factor.

From a study of this material it seems justifiable to conclude that the routine administration of vitamin K during labor in no way affected the infant mortality or stillbirth rate in the Chicago Lying-in Hospital. The mortality rates for liveborn infants of 13.5 (1941-1942) and 13.5 (1943-1944) and the stillbirth rates of 16.4 (1941-1942) and 12.3 (1943-1944) per 1,000 births compare very favorably with mortality rates reported from any obstetric hospital. The mortality rates are as low as any which to my knowledge have been reported from a large maternity service.

The question is raised as to the validity of a diagnosis of hemorrhagic disease unrelated to trauma, anoxia, or some other pathologic state. Clifford stated that 50 per cent of his 69 infants with hemorrhagic disease were sufficiently asphyxiated to require artificial resuscitation, and among the cases of authors who stress the importance of hemorrhagic disease as a cause of death the incidence of intracranial hemorrhage is always high.

According to Waddell, "Obstetric trauma in some instances is the precipitating factor in intracranial hemorrhage, thus initiating hemorrhage in an infant that is by reason of prothrombin deficiency a potential bleeder." It is the feeling in the Chicago Lying-in Hospital that the incidence of intracranial hemorrhage is directly related to the skill and judgment of the obstetrician, and that instead of being a common cause of death it should be low, and become constantly lower. Whether it is justifiable to accept the concept of hemorrhagic disease as an entity entirely unrelated to some inciting factor other than a prolongation of prothrombin time seems open to question.

It is possible that the few infants who received vitamin K during 1943-1944 may have been benefited. As stated before, it was given because it was known to be harmless and because it might possibly do some good. In no case was a diagnosis of hemorrhagic disease made (except possibly the two fatalities previously mentioned) and at no time in the past four years has any infant (except one of these fatal cases) been transfused for loss of blood by hemorrhage.

Conclusion

Evidence has been produced by many investigators which leaves no doubt (1) that in the majority of infants the prothrombin time is prolonged during the greater part of the first week of life beyond that which is normal for the adult, (2) that the administration of vitamin K to the mother prior to delivery or to the infant after birth will usually prevent the customary prolongation, (3) that after prolongation has once occurred, administration of vitamin K will usually cause a return to normal.

There is no proof, however, that prolongation of prothrombin time is a direct cause of hemorrhage. Many infants with excessively prolonged prothrombin time show no evidence of hemorrhage, while others with relatively little prolongation bleed severely. Since almost all infants show some prolongation of prothrombin time during the first week, all who bleed from any cause would be expected to show some abnormality.

The optimistic prophecies which were made early in the study of vitamin K in regard to prevention of hemorrhage and reduction in mortality rates following routine administration of vitamin K do not seem to have materialized. The present study, as well as the investigations of Sanford et al. and Parks and Sweet, indicate that in a carefully studied group of infants anything which can be considered hemorrhagic disease is extremely rare, and that the incidence of the hemorrhages which do occur in this age group is not modified by administration of vitamin K to the mother prior to delivery, or to the infant after birth.

In the present study, which was carried on for almost four years, 6,560 infants weighing over 1,000 grams were born during the two years in which vitamin K was given, and 6,630 were born during the next twenty-two months. The total fetal and infant mortality rate of 29.8 for the first two years is higher than that of 25.8 for the last two years in spite of the fact that no change of significance occurred in the incidence of primiparity, premature delivery, mode of delivery, or other known factor. The mortality rates for liveborn infants are identical in the two series, as are also the numbers of infants who showed evidence of hemorrhage on postmortem examination.

The conclusion seems justified that no decrease in infant or fetal mortality can be expected to result from the routine administration of vitamin K to all women during labor.

References

1. Ballou, O.: *Schweiz. med. Wehnschr.* 72: 1119, 1942. (Abst., Greenhill, *AM. J. OBST. & GYNEC.* 46: 908, 1943.)
2. Beck, A. C., Taylor, S., and Colburn, R. F.: *AM. J. OBST. & GYNEC.* 41: 465, 1941.
3. Bohlender, G. P., Rosenbaum, W. M., and Sage, E. C.: *J. A. M. A.* 116: 1763, 1941.
4. Brinkhous, K. M., Smith, H. P., and Warner, E. D.: *Am. J. M. Sc.* 193: 475, 1937.
5. Bruchsalter, F. S.: *J. Pediat.* 18: 317, 1941.
6. Capon, N. B.: *Lancet* 2: 887, 1932.
7. Capon, N. B.: *Lancet* 1: 602, 1942.
8. Clifford, S. H.: *J. Pediat.* 8: 367, 1936.
9. Clifford, S. H.: *J. Pediat.* 14: 333, 1939.
10. Clifford, S. H.: *J. Pediat.* 20: 650, 1942.
11. Dam, H.: *Journal-Lancet* 63: 353, 1943.
12. Editorial: *Lancet* 1: 481, 1942.
13. D'Esopo, D. A., and Marchetti, A. A.: *AM. J. OBST. & GYNEC.* 44: 1, 1942.
14. Fiechter, N.: *Schweiz. med. Wehnschr.* 72: 1252, 1942. (Abst., Greenhill, *AM. J. OBST. & GYNEC.* 46: 907, 1943.)
15. Fitzgerald, J. E., and Webster, A.: *AM. J. OBST. & GYNEC.* 40: 413, 1940.
16. Fitzgerald, J. E., and Webster, A.: *J. A. M. A.* 119: 1082, 1942.
17. Gellis, S. S., and Lyon, R. A.: *J. Pediat.* 19: 495, 1941.
18. Grossman, A. M.: *J. Pediat.* 19: 205, 1941.
19. Hardwicke, S. H.: *J. Pediat.* 24: 259, 1944.
20. Hellman, L. M., and Shettles, L. B.: *South. M. J.* 35: 289, 1942.

21. Hellman, L. M., and Shettles, L. B.: *Bull. Johns Hopkins Hosp.* 65: 138, 1939.
22. Hellman, L. M., Shettles, L. B., and Eastman, N. J.: *AM. J. OBST. & GYNEC.* 40: 844, 1940.
23. Huber, C. P., and Shrader, J. C.: *AM. J. OBST. & GYNEC.* 41: 566, 1941.
24. Javert, C. T.: *AM. J. OBST. & GYNEC.* 40: 453, 1940.
25. Javert, C. T., and Moore, R. A.: *AM. J. OBST. & GYNEC.* 40: 1022, 1940.
26. Kato, K.: *Clinics* 2: 33, 1943.
27. Kato, K., and Poncher, H. G.: *J. A. M. A.* 114: 749, 1940.
28. Kove, S., and Siegel, H.: *J. Pediat.* 17: 448, 1940.
29. Kove, S., and Siegel, H.: *J. Pediat.* 18: 764, 1941.
30. Kove, S., and Siegel, H.: *J. Pediat.* 19: 503, 1942.
31. Kugelmass, I. N.: *J. A. M. A.* 118: 1389, 1942.
32. Lawson, R. B.: *J. Pediat.* 18: 224, 1941.
33. Lehmann, J.: *Lancet* 1: 493, 1944.
34. MacPherson, A. I. S., and Henderson, J. L.: *Lancet* 1: 546, 1942.
35. Mathews, G. O.: *Bull. Vancouver M. A.* 18: 342, 1942.
36. McReady, L. L., Callahan, E. T., and Grandin, D. J.: *AM. J. OBST. & GYNEC.* 42: 398, 1941.
37. Mull, J. W., Bill, A. H., and Skowronska, H.: *J. Lab. & Clin. Med.* 26: 1305, 1941.
38. Nygaard, K. K.: *Acta obst. et gynec. Scandinav.* 19: 247, 1939.
39. Owen, C. A., Hoffman, G. R., Ziffren, S. E., and Smith, H. P.: *Proc. Soc. Exper. Biol. & Med.* 41: 181, 1939.
40. Parmalee, A. H.: *J. Michigan M. Soc.* 42: 455, 1943.
41. Parks, J., and Sweet, L. K.: *AM. J. OBST. & GYNEC.* 44: 432, 1942.
42. Poncher, H. G.: *Advances in Pediat.* 1: 151, 1942.
43. Poncher, H. G.: *J. Pediat.* 20: 637, 1942.
44. Poncher, H. G., and Kato, K.: *J. A. M. A.* 115: 14, 1940.
45. Portes, L., and Varangot, J.: *Presse méd.* 49: 812, 1941.
46. Potter, E. L.: *AM. J. OBST. & GYNEC.* 45: 1054, 1942.
47. Quick, A. J.: *Wisconsin M. J.* 38: 746, 1939.
48. Quick, A. J.: *J. A. M. A.* 118: 999, 1942.
49. Quick, A. J., and Grossman, A. M.: *Proc. Soc. Exper. Biol. & Med.* 40: 647, 1939; 41: 227, 1939.
50. Quick, A. J., and Grossman, A. M.: *Am. J. M. Sc.* 199: 1, 1940.
51. Richardson, F. H.: *Hygeia* 21: 254, 1943.
52. Richdof, L. F., and Kearney, W.: *Journal-Lancet* 62: 155, 1942.
53. Roberts, M. H.: *J. A. M. A.* 113: 281, 1939.
54. Rodda, F. C.: *J. A. M. A.* 75: 452, 1920.
55. Russell, H. K., and Page, R. C.: *Am. J. M. Sc.* 202: 355, 1941.
56. Sage, E. C.: *Nebraska M. J.* 27: 314, 1942.
57. Salomonsen, L., and Nygaard, K. K.: *Acta paediat.* 27: 209, 1939.
58. Sanford, H. N., Morrison, H. J., and Wyatt, L.: *Am. J. Dis. Child.* 43: 569, 1932.
59. Sanford, H. N., and Leslie, E. I.: *J. Pediat.* 12: 16, 1938.
60. Sanford, H. N., Shmigelsky, I., and Chapin, J. M.: *J. A. M. A.* 118: 697, 1942.
61. Scobbie, E.: *Arch. Dis. Childhood* 17: 175, 1942.
62. Shettles, L. B., Delfs, E., and Hellman, L. M.: *Bull. Johns Hopkins Hosp.* 65: 419, 1939.
63. Snelling, C. E.: *J. Pediat.* 17: 615, 1940.
64. Snelling, C. E., and Nelson, W.: *J. Pediat.* 17: 615, 1940.
65. Snelling, C. E., and Nelson, W.: *J. Pediat.* 22: 77, 1943.
66. Toohey, M.: *Arch. Dis. Childhood* 17: 187, 1942.
67. Townsend, C. W.: *Arch. Pediat.* 11: 559, 1894.
68. Tyson, R. M.: *AM. J. OBST. & GYNEC.* 37: 241, 1939.
69. Valentine, E. H., Reinhold, J. G., and Schneider, E.: *Am. J. M. Sc.* 202: 359, 1941.
70. Vollmer, H., Adler, C., and Altman, H. S.: *Am. J. Dis. Childhood* 64: 462, 1942.
71. Waddell, W. W.: *J. Pediat.* 20: 656, 1942.
72. Waddell, W. W.: *J. A. M. A.* 118: 1389, 1942.
73. Waddell, W. W., and Guerry, Du P., III: *J. A. M. A.* 112: 2259, 1939.
74. Waddell, W. W., and Lawson, G. M.: *J. A. M. A.* 115: 1416, 1940.
75. Warner, E. D.: *M. Clin. North America* 27: 371, 1943.
76. Webster, A., and Fitzgerald, J. E.: *S. Clin. North America* 23: 85, 1943.
77. Willumsen, H. C., Stadler, H. E., and Owen, C. A.: *Proc. Soc. Exper. Biol. & Med.* 47: 116, 1941.

7 THE CONSERVATIVE MANAGEMENT OF SOME VARIETIES OF PLACENTA PREVIA*

HERMAN W. JOHNSON, M.D., F.A.C.S., HOUSTON, TEXAS

*(From the Department of Obstetrics, Baylor University College of Medicine, and the
Maternity Division of St. Joseph's Infirmary)*

THE main purpose of this paper is an attempt to drive away some of the goblins which have long, long ago been drawn into the picture of placenta previa and have been handed down from one edition to the next edition of acceptable textbooks on obstetrics with no evidence of revision commensurate with increased clinical experience. A second purpose is to urge most conservative measures when the decision is made to effect delivery per vaginam.

Vigorous protest should be made against continuously inculcating into the minds of medical students and of practicing physicians the impression that a case of placenta previa can end fatally as a direct result of the first blood loss, or even of any subsequent bout of bleeding, when no attempt at delivery has been made.

The following quotations from obstetric textbooks in common usage today exemplify the outmoded statements referred to above. Stander-Williams,¹ "Ordinarily the initial bleeding is rarely so profuse as to prove fatal, and ceases spontaneously, to recur again when least expected. . . . In a certain proportion of cases, particularly when the insertion is marginal, the bleeding does not appear until the time of labor, when it may vary from a slight bloodstained discharge to a profuse or even fatal hemorrhage." DeLee-Greenhill,² "The first hemorrhage may vary from a few drops, hardly a stain on the linen, to a profuse 'flooding,' which may be fatal at once, but usually a few ounces are lost as the initial symptom." Beck,³ "The initial loss of blood is quite profuse and often alarming. Fortunately, however, it seldom is fatal."

The inference from these acceptable authors is that the spontaneous bleeding from placenta previa sometimes is fatal. It is the author's opinion that the obstetrician should not approach or behold a case of placenta previa with this unwarranted fear in his mind, since such an attitude might cause him to resort to measures in treatment which might be too drastic or untimely. Furthermore, these same authors importune the physician to terminate the pregnancy as soon as the diagnosis of placenta previa has been made. This appears unwarranted. There would seem to be no good reason for sacrificing the life of a fetus merely because its placenta happened to be implanted over or near the cervical os. More particularly is this true when the claimed serious threat to the life of the mother is still unproved. The high fetal mortality in placenta previa cannot be reduced unless the pregnancy is allowed to proceed into the period of viability and until the practice of using the body of the fetus as a mechanical tampon is discontinued.

It is essential to proper treatment that all means at our command be used for the purpose of making a correct diagnosis. The assumption that vaginal bleeding at term or during the last trimester is due to placenta previa is grossly erroneous. Moreover, it should be constantly borne in mind that only about 33 per cent of such cases of bleeding are actually due to placenta previa.

*Read before the Fifteenth Annual Meeting of the Texas Association of Obstetricians and Gynecologists, Nov. 22, 1944, Dallas, Texas.

Further evidence in support of the low incidence of placenta previa in cases presenting varying amounts of vaginal bleeding is found in the following quotation from a statistical report by Dippel and Brown,⁴ "As a matter of fact, there were only eleven instances of clinical placenta previa in the group, while the remaining fifteen were merely roentgenologic instances of low implantation of the placenta. There were only two cases where clinical evidence of premature separation of the normally implanted placenta was present. Therefore, if cesarean section had been routinely performed on all cases of vaginal bleeding on the assumption that they had either placenta previa or premature separation of the placenta, that assumption would have been erroneous, and cesarean section would have been unjustifiably performed in 85.87 per cent of the cases."

For obstetricians it might be well to reverse the dictum which ends "... is due to placenta previa unless proven otherwise," to "... is due to other causes unless proven placenta previa." This suggested change does not mean that the obstetrician should become less insistent upon making an accurate diagnosis in all cases of vaginal bleeding.

Two methods of localizing the placenta are available, namely, x-ray visualization and manual examination. All cases of suspected placenta previa should have the benefit of both. Needless to say, the element of error will be decreased with the skill of those making the examinations. The great advantage of roentgen localization of the placenta has been amply shown by Dippel and Brown.⁴ They were able to visualize the placenta 236 times out of 262 observations, an incidence of 90 per cent. Unfortunately, the assistance of skilled observers in placental visualization is not generally available and unskilled interpretations are dangerous. A reliable interpretation, when available, serves as a check on the vaginal examination, i.e., it is further proof of where the placenta is or is not.

It is the author's opinion that a sterile vaginal examination is essential for accurate diagnosis. This should be done in all suspected cases and done whether there is bleeding or not. Rectal examinations are contraindicated, as zeal for information may cause too much trauma. Naturally, the vaginal examination should be done with due consideration for the exigencies of the case, and with extra precaution against infection. As for preparedness for delivery or transfusion at the time of this examination, more will be said later.

The vaginal examination means nothing to fingers that have not palpated hundreds of perfectly normal cases late in pregnancy and in labor, because only normal findings can be used to evaluate departures from the normal. The trained finger knows the usual station of the head, the usual station of the body of the cervix; and if not in labor, the degree of ripening of the cervix and the location of its internal os. If in labor, the amount of effacement or dilatation is known. The trained examiner knows that the lower uterine segment is very thin and through it the presenting pole may be easily palpated for some distance lateral, as well as posterior and anterior to the cervical os. Normally, throughout this area nothing save varying quantities of amniotic fluid is interposed between the fingers and the presenting pole. If a mass is interposed, however, its thickness, extent, and location will be of great significance. Thus, without even invading the cervix, it may be possible to make a reasonably accurate diagnosis of the various degrees of placenta previa from low implantation of the placenta to placenta previa centralis. On the other hand, in multiparas in labor, with effacement of the canal and some dilatation of the external os, the finger may be gently inserted in quest of a place where only membranes are felt and for the purpose of rupturing them. If one is fortunate enough to have x-ray interpretations and a careful vaginal exami-

nation to fit into the clinical picture, the percentage of error in the diagnosis of placenta previa should be very small.

Some apology should be made for reciting so much elementary obstetrics, but it has occurred to me many times that the books have not laid enough stress on normal findings in the differential diagnosis of abnormal conditions.

The forces of labor are not altered in placenta previa; therefore, in the nontoxic cases (the combination of previa and toxemia is extremely rare) there would be no reason to suspect any difference in the process of effacement, dilatation, placental separation and expulsion, except that as dilatation progresses, uteroplacental sinuses are abrupted and this is accompanied by intermittent bleeding.

The amount of bleeding at any given time is largely dependent on the amount of dilatation occurring at that moment, since it is the cervical dilatation that causes the abruption. This is not true of the centralis variety. When the hemorrhage is profuse, with little or no dilatation, one may be reasonably certain that he is dealing with a case of the central type.

Fortunately, the time required to complete the first stage of labor is at least four hours. The bleeding is intermittent and, as mentioned, is caused by the periods of dilatation and not directly by the labor pains. The foregoing statement might be open to question, but everyone who has observed dilatation carefully must feel that the progress of dilatation varies in every labor and in different periods in each labor. These periods of progress seem not to take place with each pain but, when they occur, represent the accumulative effect of many pains. Fibroelastic tissue may require a process of softening between each period of dilatation. Perhaps this mechanism is a lifesaver in placenta previa, because it permits nonbleeding periods, i.e., periods which allow the patient to regain some blood volume. If the foregoing concept of the mechanics of separation in placenta previa is true, it permits of two reasonable conclusions: first, that a careful vaginal examination cannot simulate a series of labor pains building up to a period of dilatation and separation with hemorrhage. The examination may be coincidental with the period of dilatation and bleeding, but not the cause. This may be easily proved by making another examination immediately following the cessation of the current bleeding. Second, a patient at or near term going into labor might require four hours or more to complete the first stage. If she lost 1,500 c.c. during this entire period, it would mean a steady blood loss of 6 c.c. per minute, but if the loss were at intervals of ten minutes, the periodic amount lost would be 60 c.c. This long range intermittent loss of blood with its opportunities for natural and for transfusion replacement could hardly prove lethal. Therefore, the conclusion seems reasonable that there is little danger of the patient's bleeding to death, provided active measures to effect delivery of the baby or placenta are not taken.

The fetal mortality in placenta previa will always be high. Naturally, it would be expected to be lowest in deliveries effected by cesarean section; but even here we should be reluctant to promise the family a living and well baby. The incidence of fetal abnormalities associated with placenta previa, as shown by Greenhill,⁵ is considerable. In another group of cases the fetus will have suffered some asphyxia from excessive interference with uteroplacental circulation, and with the least amount of inhalation anesthesia, it may rapidly develop an asphyxial hemorrhage and die soon after delivery.

There is not sufficient data available at the present time to show how much decrease in fetal and maternal mortality may be accomplished by using, in vaginal deliveries, the strictly conservative treatment as opposed to the version, scalp traction, bagging, or other techniques. Watson⁶ reported a small series showing improvement. In our small series of private cases, the conservative treatment has been employed with a fetal mortality much less than the usual percentage given for vaginal deliveries.

In Table I is recorded the material from the St. Joseph's new Maternity Division. It has been divided into two separate time intervals since the earlier period supplied data for a presentation before a local gathering of physicians. The more recent period, then, brings the data up to date. The great differences in incidence of placenta previa in the two time periods are not readily explainable. Only the incidence in the past year corresponds favorably with that reported by Stander⁷ for the New York Lying-In Hospital. It is most probably the true incidence for our hospital service since the records recently have been more accurately kept. In this connection, it should be pointed out that the staff of the St. Joseph's Maternity is heterogeneous though fairly well controlled by an organized consultation system.

TABLE I. INCIDENCE OF PLACENTA PREVIA IN TERM AND NEAR TERM DELIVERIES AT ST. JOSEPH'S MATERNITY

Deliveries 1939 to October, 1943	19,588
Number of cases of placenta previa	48
Incidence 1 in 408	
Deliveries October, 1943, to October, 1944	5,038
Number of cases of placenta previa	31
Incidence 1 in 162	
Deliveries 1939 to October, 1944	24,626*
Number of cases of placenta previa	79
Incidence 1 in 347 (Stander, 1 in 180)	

*211 sets of twins.

TABLE II. CORRECTED FETAL MORTALITY IN 79 CASES OF VARIOUSLY TREATED PLACENTA PREVIA (82 FETUSES)

METHOD OF DELIVERY	CASES (NO.)	DEATHS (NO.)	FETUSES (NO.)	TOTAL MORTALITY (%)
Cesarean section	42	9	42	21.4
Strictly conservative	29	2	24	8.3
Other techniques	8	5	6	83.3
Totals	79	16	72	22.2

Returning now to fetal mortality as experienced in our largest maternity hospital, Table II, it is seen that corrected figures are given. Only the following ten fetuses were corrected out; prematurity, i.e., less than seven full calendar months gestation (seven cases), stillbirths (two cases, both of which were macerated, one being a case of missed labor), and congenital anomalies incompatible with life (one case). The relatively high mortality for cesarean section deliveries, which is essentially that of the entire series, is discouraging and probably accounted for through the effect of anesthetic agents upon already traumatized fetuses. By strictly conservative treatment is meant no interference with labor or delivery except possibly rupture of membranes, elective low forceps, or breech extraction after full cervical dilatation. This method of handling labor and delivery, exclusive of transfusions or other supportive therapy equally applicable to all other cases, yielded the lowest fetal mortality rate. The worst rate is found in the group treated by other techniques, i.e., all other methods of vaginal delivery. Some of these latter,

notably the intrauterine bag, may have some merit in selected cases. However, others, particularly version with extraction through an incompletely dilated cervix (two cases) and Dührssen's incisions with operative delivery (one case), are to be severely and forever condemned. It must be conceded that the number of cases here presented, and especially the number in each subdivision of type of delivery, is too small to be of absolute statistical value. Nevertheless, each shows a definite trend which cannot be ignored.

The immediate maternal mortality in all cases of placenta previa should be nil or at least should not exceed 1 per cent. Here the cause of death is due to hemorrhage and is seldom, if ever, due to the blood loss of previa alone, but to some additional factor which increases the blood loss, e.g., untimely cesarean section, injury to the cervix, rupture of uterus, and too hasty separation of the placenta during the third stage. There are two rare complications of placenta previa which might prove immediately fatal, namely, massive ablation, and placenta accreta involving the cervix. The remote maternal mortality which is due to infection, though small, will always be present. Even here anemia from blood loss may be a contributing factor through lowering resistance. The maternal mortality in our relatively small total series was nil from all types of delivery.

All cases of suspected placenta previa should be hospitalized for purposes of accurate diagnosis and for close observation of a developing anemia. Hospital rest may also decrease the bleeding episodes while awaiting good viability of the fetus. If, for economic reasons, this is impractical, the patient should be returned to the hospital for careful blood study after each bleeding spell of any consequence.

When the pregnancy is terminated either with the onset of labor or by prearrangement, it will, for purposes of treatment, fall into one of two groups, namely, those best delivered by cesarean section and those best delivered per vaginam. The first group includes all cases of central placenta previa and probably, in the interest of the baby, practically all previas in primiparas. This arrangement leaves for the second group those cases of partialis and marginalis occurring in multiparas. In the first group it is imperative only that the operator make sure that the operation is done at the safe time, i.e., that the blood pressure be sufficiently high to withstand the sudden additional blood loss following separation of the placenta. Furthermore, the anesthetic should be as light and short as possible and the one which is least conducive to circulatory collapse.

Inasmuch as the incidence of placenta previa increases with multiparity, the second group will include a large number of cases. It is for this group that the writer strongly advocates the ultraconservative treatment as opposed to bagging, version, scalp traction, etc. It is helpful for one using it to have the earnest and positive conviction that untraumatized and unhurried previas do not bleed to death. Otherwise, a puddle of blood may cause one to change the treatment at the wrong time and with dire consequences.

The patient is taken to the delivery room and prepared and draped for delivery. This is not done with the idea that delivery or transfusion may be necessary, but because the delivery room is the cleanest and handiest place to rupture the membranes. With the utmost care the middle finger of the left hand seeks a place near the edge of the placenta where the membranes alone separate the finger from the presenting fetal pole. Using the finger as a director, uterine dressing forceps are passed to contact the membranes.

Then, instead of puncturing them, the tips are used to bite a perforation. The forceps are inserted further and opened in order to produce a large rent. This allows the amniotic fluid to escape freely. The patient is returned to her room. As labor progresses, the presenting pole aids the dilatation and acts as a natural tampon. In addition, the escape of the amniotic fluid decreases the intrauterine volume and permits of at least a certain amount of retraction in the lower uterine segment. This may be a valuable aid in preventing blood loss. The labor is then watched with frequent checking of the blood loss, blood pressure, and fetal heart. Everything should be done to make the labor as comfortable and slow as possible. It should not be necessary to say that a suitable donor whose Rh possibilities have been determined should be available. Plasma may be used to great advantage during the emergency, reserving the blood donor for the treatment of a possible postpartum hemorrhage or anemia.

The patient is returned to the delivery room at the end of the first stage of labor. At the completion of the second stage, which may end spontaneously or be assisted with outlet forceps delivery, the uterus may be gently supported, but no effort should be made to hasten separation of remaining attached placental tissue. This is especially true if free bleeding is present. There is no blood escaping from unabrupted uteroplacental sinuses, and to provide a fresh source of bleeding may be the determining factor in the outcome. Allow the placenta to separate naturally.

It is not presumed that every patient with a nonviable fetus and placenta previa should be carried along indefinitely. The tendency has always been to interfere at too early a stage in pregnancy. Our contention, however, is that it is safe for both mother and child, provided the mother's blood picture is followed carefully. This must be the criterion for interruption of the pregnancy before the fetus has reached easy viability, and not an alarming history derived from a lay estimate of the amount of blood lost. Procrastination must end when the total blood loss has produced a secondary anemia of such severity that further bleeding would endanger the life of the mother.

In conclusion, may I, for statistical purposes, make the following request? will you please report to me any fatal case of placenta previa which you may know about where there had been no cervical nor intrauterine manipulation, nor any attempt at manual removal of remaining placental tissue during the third stage of labor. I promise to reward you and will add your case to my series. This offer has been made many times during the last fifteen years, and at many of the "refresher courses" offered by the State of Texas several years ago. These courses were attended by many of the older practitioners. I have, as yet, no case with which to start the series. Certainly, somewhere, sometime, someone must have died from placenta previa without having received energetic or heroic treatment.

Conclusions

1. It is suggested that obstetric textbooks be revised as regards maternal prognosis in placenta previa.
2. No maternal death from placenta previa has been seen where Nature has been allowed to take its course as regards labor and delivery.
3. All cases of vaginal bleeding in the last trimester should be subjected to careful examination in the hospital with the view to rule out placenta previa.
4. Vaginal examination is essential for accurate diagnosis, but there are several valuable aids whose merits are presented.

5. The mechanics of cervical dilatation and of placental separation in placenta previa are discussed.

6. Reasons for the improbability of a patient spontaneously bleeding to death from placenta previa are given.

7. Hospitalization from the first episode of vaginal bleeding through labor and delivery is urged.

8. The maternal mortality for all types of delivery in the small series reported (79 cases) was nil.

9. The fetal mortality was average in cesarean section deliveries. It was lowest in conservative vaginal deliveries.

References

1. Stander, H. J.: Williams Text-Book of Obstetrics, ed. 8, New York, 1941, D. Appleton-Century Co., p. 1061.
2. Greenhill, J. P.: Principles and Practices of Obstetrics, ed. 8, Philadelphia, 1943, W. B. Saunders Co., p. 459.
3. Beck, Alfred: Obstetrical Practice, ed. 3, Baltimore, 1942, Williams & Wilkins Co., p. 696.
4. Dippel, A. L., and Brown, W. H.: AM. J. OBST. & GYNEC. 40: 986, 1940.
5. Greenhill, J. P.: AM. J. OBST. & GYNEC. 37: 624, 1939.
6. Watson, B. P.: AM. J. OBST. & GYNEC. 46: 524, 1943.
7. Stander, H. J.: Williams Text-Book of Obstetrics, ed. 8, New York, 1941, D. Appleton-Century Co., p. 1058.

RESULTS OF VARIOUS TYPES OF TREATMENT IN ADENOCARCINOMA OF THE ENDOMETRIUM

CHAS. E. McLENNAN, M.D., PH.D., SALT LAKE CITY, UTAH

(From the Departments of Obstetrics and Gynecology, University of Minnesota and University of Utah Schools of Medicine, and the University of Minnesota Hospitals, Minneapolis)

DURING the years 1928 to 1943, inclusive, 225 women with carcinoma in the body of the uterus were observed in the University of Minnesota Hospitals. Of these, 111 were seen more than five years ago; 114 were handled after Jan. 1, 1939, and are considered separately, since they have not passed through the required five-year observation period. All of these patients have been followed to the present time or until death. In all instances histologic proof of the carcinoma was obtained. Fifty of the 111 were living and free from recurrence five years after treatment, an absolute cure rate of 45 per cent. The relative cure rate, based on 106 patients given some form of therapy, is 47 per cent. Since only 80 of the 111 patients were treated primarily at the University Hospital, while 31 had had some form of treatment elsewhere, the material has been divided into these two groups for detailed consideration. Seventy-six of the 80 women *not previously treated* were given therapy at the University Hospital, and 34 were living and free from recurrence five years after treatment. Thus, the relative cure rate for this group is 44.7 per cent and the absolute cure rate 42.5 per cent.

Material

Table I shows the varieties of treatment given to the 80 patients referred without preliminary therapy. More than half (46) of these were treated by irradiation alone (radium and/or x-ray). Five others were treated initially with radium and x-ray, hyster-

ectomy being done from one and one-half to six years later because of local recurrences. The reasons for not performing hysterectomy in the 46 patients treated by irradiation alone are shown in Table II. It will be seen that 26 patients were considered inoperable on the basis of actual or possible extension of carcinoma beyond the uterine corpus. Only 13 of these had proven metastases (largely vaginal), the other 13 presenting some induration in the broad ligament areas. In view of the comparatively poor end results in the irradiated group, it may have been advisable, in retrospect, to have subjected to laparotomy most of the patients with minor metastases and certainly all who exhibited merely questionable thickening in the broad ligaments. The five-year cure rate for 29 patients subjected to total hysterectomy (Table I, items 1-5) was 83 per cent, whereas only 22 per cent of the 46 irradiated patients lived more than five years. The latter group, of course, contained all of the surgically "bad risk" patients, as well as those with extensive tumors, but it seems likely that a much greater percentage of the patients could have withstood operation successfully. On the basis of our experience in the past five years, it appears that approximately 30 per cent of patients with carcinoma of the fundus are not good candidates for surgical therapy when first seen.

Table III gives the end results for 31 patients treated to some extent before presenting themselves at the University Hospital. While one might anticipate poor results in this group, the five-year cure rate of 57 per cent does not confirm this expectation. The good result in the small group treated by subtotal hysterectomy elsewhere is particularly surprising, but presumably represents the fact that these lesions, fortunately, were early and well localized. The apparently favorable outcome in this group should not by any means be interpreted as an indication for subtotal removal of the uterus in carcinoma of the fundus. Those receiving radium elsewhere were, for the most part, treated similarly to those treated primarily in the University Hospital (i.e., x-ray or hysterectomy following radium) and the results are comparable to those in the primary group. The 12 patients

TABLE I. ADENOCARCINOMA IN CORPUS UTERI, 1928 TO 1938: VARIETIES OF THERAPY IN PATIENTS NOT PREVIOUSLY TREATED ELSEWHERE

TREATMENT	NO.	5-YEAR CURE RATE (%)
1. Radium, x-ray, total hysterectomy	1	100.0
2. Radium, hysterectomy, postoperative x-ray	17	82.3
3. Hysterectomy, postoperative x-ray	3	100.0
4. Radium, hysterectomy (1 postoperative death)	3	66.7
5. Radium, x-ray; hysterectomy for recurrence 1½ to 6 years later	5	80.0
6. Subtotal hysterectomy, postoperative radium and x-ray	1	0.0
7. X-ray followed by radium	4	0.0
8. Radium followed by x-ray	38	26.3
9. X-ray only	4	0.0
10. No treatment	4	0.0

TABLE II. ADENOCARCINOMA IN CORPUS UTERI, 1928 TO 1938. REASONS FOR USING ONLY IRRADIATION IN 46 CASES

REASONS	NO. OF CASES
1. Actual or possible extension of tumor beyond body of uterus	26
2. Old age (over 70 years)	7
3. Diabetes mellitus	5
4. Pelvic inflammation following radium	2
5. Corpus tumor mistaken for primary cervical tumor	2
6. Heart disease	2
7. Carbuncle of abdominal wall	1
8. Obesity (330 pounds) and hypertension	1

TABLE III. ADENOCARCINOMA IN CORPUS UTERI, 1928 TO 1938. RESULTS IN PATIENTS TREATED TO SOME EXTENT ELSEWHERE

TREATMENT ELSEWHERE	NO.	LIVING 5 YR. AFTER TREATMENT HERE	5-YEAR CURE RATE PER CENT
Total hysterectomy	12	5	41.7
Subtotal hysterectomy	9	7	77.8
Radium in uterine cavity	10	5	50.0
Total	31	17	56.7*

*Relative rate, based on 30 patients given further treatment.

who had had total hysterectomy done elsewhere were admitted largely because of vaginal metastases. *Irradiation salvaged 42 per cent of these for at least five years.*

During the years 1939 to 1943, inclusive, 114 new patients with carcinoma of the uterine body were observed. Twenty-one of these women had been subjected to some form of therapy elsewhere. Table IV shows the nature of the treatment given to the 93 patients who had not been treated previously. Tables V and VI reveal the reasons for incomplete therapy in 27 instances and nonroutine management in 17 other patients. From the beginning of 1939 until July 1, 1941, standard or "routine" therapy for carcinoma in the uterine corpus consisted of deep x-ray, intrauterine radium, and total hysterectomy, in that order. The dosage of x-ray amounted to 250 to 300 per cent skin-erythema dose delivered to the site of the tumor in 25 to 30 daily treatments over approximately four weeks. Radium then was applied from five intrauterine portals, and a dose of 5,000 mg. hours was given over a period of 100 hours. Four to six weeks after the completion of the irradiation therapy, total hysterectomy and bilateral salpingo-oophorectomy were carried out by the abdominal route.

It should be noted that only 53 per cent of the patients received "routine" treatment. In other words, in nearly half of the patients there were reasons for breaking through a carefully planned therapeutic sequence. While it is true that approximately 70 per cent of the patients were subjected to "complete" or adequate therapy, in the sense that total removal of the uterus was effected, it is obvious that the treatment in some of these women cannot be viewed as satisfactory from the standpoint of having eradicated all the demonstrable malignant tissue. Thus, something between 50 and 70 per cent of the previously untreated patients may be said to have a chance of five-year survival on the basis of treatment instituted when first seen. That is, at least 50 per cent but not over 70 per cent of the patients received a form of therapy designed to be completely curative. In material of this sort it seems unreasonable to anticipate anything better than a five-year cure rate of *about* 60 per cent, and even this would entail an almost perfect end result in those without obvious metastases at the time of treatment.

Table VII shows the present status of the 114 women seen in the last five years. Only one patient receiving "routine" treatment has died from recurrent carcinoma. This 65-year-old woman was treated in June, 1942, with our present routine of radium followed by hysterectomy, and died in September, 1943, with a massive recurrence of pelvic carcinoma. One routinely treated patient died postoperatively of bronchopneumonia after the abdominal wound had separated completely on two occasions. She had been treated with a full course of x-ray as well as radium preoperatively. A third patient in the routinely treated group died of heart disease two and one-half years after treatment of the carcinoma. Autopsy showed no evidence of recurrent tumor. Only one-fourth of the patients receiving incomplete therapy have survived from 0 to 4 years and the ultimate five-year survival in this group may be ex-

TABLE IV. ADENOCARCINOMA IN CORPUS UTERI, 1939 TO 1943. THERAPY GIVEN 93 PREVIOUSLY UNTREATED PATIENTS

TREATMENT	NO.	PER CENT OF TOTAL
1. "Complete" treatment: hysterectomy with or without irradiation	66	70.9
X-ray, radium, hysterectomy	22	
Radium and hysterectomy	27	
Hysterectomy alone	11	
X-ray and hysterectomy	3	
Hysterectomy, postoperative radium	1	
Hysterectomy, postoperative x-ray	1	
Radium (partial dose), hysterectomy, postoperative x-ray	1	
2. "Routine" treatment: radium \pm x-ray, total hysterectomy in 4 to 6 weeks	49	52.6
3. Other varieties of treatment	27	29.1
Intrauterine radium only	12	
x-ray and radium	6	
X-ray only	2	
Exploratory laparotomy	1	
Subtotal hysterectomy, postoperative x-ray and radium	1	
Subtotal hysterectomy (extensive metastases at operation)	1	
No treatment	4	

TABLE V. ADENOCARCINOMA IN CORPUS UTERI, 1939 TO 1943. REASONS FOR INCOMPLETE THERAPY IN 27 PATIENTS

REASONS	NO. OF CASES
1. Obvious metastases when first examined	9
2. Heart disease	6
3. Obesity and hypertension	3
4. Primary malignant disease elsewhere	2
5. Irradiation death prior to hysterectomy	2
6. Advanced age (75 years or above)	2
7. Uremia following irradiation (death)	1
8. Operation refused	1
9. Multiple sclerosis	1

TABLE VI. ADENOCARCINOMA IN CORPUS UTERI, 1939 TO 1943. REASONS FOR NONROUTINE THERAPY IN 17 PATIENTS

REASONS	NO. OF CASES
Uterus perforated during attempt at radium insertion	1
Curetage negative (false cavity made in wall) ; hysterectomy without preliminary radiation	1
Myomata uteri	2
Vaginal metastases present, others suspected	2
Pelvic inflammatory disease	2
Diabetes and obesity	1
Psychosis	1
Diarrhea during irradiation	1
Leucopenia during irradiation	1
Febrile reaction from radium	1
Ovarian cystoma	1
Question of primary gastric tumor (immediate laparotomy)	1
Extrauterine mass of unknown origin (metastatic tumor in iliac lymph nodes)	1
Operator's decision to omit radiation (private patient)	1

TABLE VII. ADENOCARCINOMA IN CORPUS UTERI, 1939 TO 1943. PRESENT STATUS OF
114 PATIENTS OBSERVED LESS THAN FIVE YEARS

THERAPEUTIC GROUP	NUMBER LIVING 0-4 YEARS	PER CENT OF GROUP
66 given "complete" treatment (3 deaths from intercurrent disease)	56	84.8
49 given "routine" treatment (Deaths: 1 intercurrent disease, 1 postoperative, 1 recurrent carcinoma)	46	93.8
27 given incomplete or no therapy	7	25.9
93 given no treatment elsewhere	63	67.7
21 treated elsewhere previously	14	66.7

TABLE VIII. RESULTS OF TREATMENT IN ALL CASES OF ADENOCARCINOMA IN CORPUS UTERI,
1928 TO 1943

[illegible]

pected to be exceedingly low. It is interesting to note that there is to date no difference between the survival rate of patients treated to some extent elsewhere and those treated primarily in the University Hospital. This has already been demonstrated for the patients treated prior to 1939, and is quite the opposite of our results in women with carcinoma of the uterine cervix. The results of treatment in *all* cases of carcinoma of the uterine body, in terms of absolute survival and cure rates, are depicted in Table VIII.

Table IX shows the operative mortality for all patients with adenocarcinoma of the uterine body who have been subjected to major surgical procedures. The gross surgical mortality over sixteen years has been 5.8 per cent, but when three patients with virtually hopeless prognosis prior to operation are excluded, the over-all rate becomes 3 per cent. Details concerning the six postoperative deaths are given below. It should be noted that only 24 per cent of 111 women were treated surgically from 1928 to 1938, while approximately 68 per cent of the last 114 patients were subjected to operation. The corrected primary operative mortality rate for the last five years is 1 per cent below that for the period 1928 to 1938, but the significance of this is open to serious question because of the comparatively small number of cases in the earlier group.

TABLE IX. OPERATIVE MORTALITY IN ADENOCARCINOMA IN CORPUS UTERI, 1928 TO 1943

PERIOD	NUMBER OF PATIENTS OPERATED	NUMBER OF POSTOPERATIVE DEATHS	MORTALITY RATE PER CENT
1928-1943	104	6	5.8
1928-1938	27	1	3.7
1939-1943	77	5	6.5
1939-1943, corrected*	74		2.7
1928-1943, corrected	101	2	3.0

*See explanation in text.

Postoperative Deaths

1. H. G., No. 626016, age 63 years, admitted July 16, 1934, died July 22, 1934. Had hypertensive heart disease, blood pressure 180/105. Preliminary treatment with 2,400 mg. hours of radium in March, 1934. Failed to return for hysterectomy until four months later. Became irrational on first postoperative day, temperature rose to 105° F., and death ensued on third day. Autopsy did not confirm clinical diagnoses of peritonitis and bronchopneumonia. The heart showed coronary sclerosis and there was questionable evidence of occlusion of the anterior descending branch of the left coronary artery.

2. E. C., No. 679832, age 41 years, weight 190 pounds, admitted April 19, 1939, for course of deep x-ray and radium, discharged June 6, 1939, readmitted June 27 for hysterectomy, died Aug. 3, 1939. Total hysterectomy and bilateral salpingo-oophorectomy were carried out on June 30. Complete separation of the abdominal wound occurred on the twelfth postoperative day and secondary closure was done by layers. Dehiscence recurred eight days later, at which time there was evidence of bronchopneumonia. The course was progressively worse despite oxygen, sulfonamides, and blood transfusions. Autopsy was not permitted, but inspection of the abdominal cavity through the operative site showed no gross evidence of peritonitis.

3. R. C., No. 626417, age 68 years, weight 203 pounds, had received radium and x-ray therapy in 1935 for adenocarcinoma of the uterine corpus. This therapy was repeated in 1937 when recurrent tumor appeared. She was admitted Aug. 9, 1939, for surgical treatment of a second recurrence. Following total abdominal hysterectomy on August 25 she developed a pelvic abscess and died on the tenth postoperative day. Autopsy revealed, in addition to the pelvic infection, questionable evidence of pulmonary embolism.

4. A. P., No. 688249, age 37 years, weight 288 pounds, admitted Nov. 14, 1939, with vaginal and vulvar metastases from adenocarcinoma of the uterine corpus. Exploratory laparotomy on November 28 showed extension of tumor to the aortic lymph nodes, and only a right salpingo-oophorectomy was done. She expired on the third postoperative day after a temperature rise to 108° F. Autopsy failed to reveal any explanation for the sudden death other than the clinical picture of hepatorenal syndrome.

5. M. T., No. 717690, age 67 years, weight 159 pounds, admitted Feb. 10, 1942. Hysterectomy was done on February 19 without preliminary irradiation because of the pres-

ence of an adnexal mass, which was found to be a myoma. Death on the eighth postoperative day was attributed to septicemia, although bacteriologic proof of this could not be established. Autopsy was limited to the abdominal cavity and was not helpful in establishing the cause of death.

6. I. P., No. 725559, age 55 years, admitted Oct. 18, 1942, with pelvic carcinomatosis and vaginal metastases. Laparotomy was done on October 23 to remove as much tumor as possible prior to palliative x-ray therapy. Uterine fundectomy and bilateral salpingo-oophorectomy were performed. On the thirteenth postoperative day she developed right hemiplegia, went into coma, and died five days later. Autopsy showed metastatic carcinoma in the brain and terminal acute bacterial endocarditis with splenic and renal infarcts.

Group Receiving X-ray Therapy, 1939 to 1941

From Jan. 1, 1939, to July 1, 1941, 38 patients, ranging in age from 40 to 74 years (average of 59), received full or partial courses of deep x-ray. Thirty-one were previously untreated. In three of these the x-ray was given as a palliative procedure, and complete therapy, including hysterectomy, was not contemplated. There remain, then, 28 patients to whom deep x-ray was administered as the first step in a plan of "complete" or "routine" therapy. (See above for definition.)

The entire planned therapy was completed by only 18 (64 per cent) of these patients. X-ray was discontinued in three because of nausea, vomiting, and diarrhea, and in one because of a severe leucopenia. In two, only a partial dosage of radium was given and one of these was not subjected to hysterectomy because of pelvic infection and general debility associated with advanced age. One received no radium because the uterus was accidentally perforated during an attempt at application, and in another the radium was omitted because of the severity of the gastrointestinal disturbance during a partial course of x-ray. Three patients died following irradiation before they could be subjected to hysterectomy, and no hysterectomy was done in the elderly woman mentioned above. Of the three dying soon after irradiation, one developed uremia, one had peritonitis following perforation of a radiation ulcer in the colon, and the third was a diabetic who developed a severe febrile reaction a week after completing her irradiation. She died within a few days despite adequate control of the diabetes, and permission for autopsy could not be obtained. The only obvious cause of the high fever was a pyogenic skin infection.

In the group of seven patients who had previously been treated to some extent, x-ray therapy had to be discontinued in two instances, once because of nausea and vomiting, and once because of severe diarrhea.

Secondary anemia, as indicated by a hemoglobin level of less than 10 grams per 100 c.c. of blood, developed in two patients during irradiation therapy. Leucopenia (less than 3,000 white blood cells per cu. mm.) developed in seven patients. In one of these the x-ray treatments were stopped entirely, in the others only intermittently. Twenty-one of the 38 irradiated patients had diarrhea during the therapy, 12 complained of nausea and vomiting, 3 developed evidence of acute pelvic inflammatory disease, 2 complained of persistent abdominal pain, and in one an old colostomy site, which had been closed surgically, reopened spontaneously.

Seven out of 20 uteri which were completely irradiated subsequently showed histologic evidence of viable carcinoma at the time of hysterectomy or autopsy. In 6 patients who were incompletely irradiated, 5 of the uteri contained carcinoma following hysterectomy. Further details concerning the histologic findings in our irradiated corpus tumors are reported elsewhere (Stowe). It is also interesting to note that myomata uteri were found in 7 out of the 28 patients in this series who were subjected to either hysterectomy or autopsy.

TABLE X. ADENOCARCINOMA IN CORPUS UTERI, JANUARY, 1939, TO JULY, 1941. SURVIVAL OF PATIENTS RECEIVING DEEP X-RAY THERAPY

	LIVING AND WELL 3 TO 4½ YR.	LIVING WITH RECUR- RENCE	DEAD
Entire group of 38 patients	23 (61%)	2	13
31 not previously treated	19 (61%)	2	10
7 previously treated elsewhere	4 (57%)	0	3
18 who completed full therapy	15 (83%)	1	2*
10 who had less than full therapy	4 (40%)	0	6

*One death from intercurrent disease (cardiac), one postoperative.

Table X gives the results of treatment of the 38 irradiated women in terms of survival from 3 to 4½ years after therapy. It may be seen that approximately 60 per cent have survived, and that there is no appreciable difference between the group not previously treated and the group which had been given some form of therapy elsewhere. The survival rate for the 18 who went through the complete therapeutic plan is 83 per cent. This figure would have been 100 per cent had there not been one postoperative death (wound disruption and pneumonia) and one death from heart disease (see above). Only 4 of the 10 women who were unable to complete full therapy are alive at present.

Discussion

Hysterectomy generally is conceded to be the important part of the therapy for carcinoma of the uterine body. In recent years the only objection to this concept has been raised by Heyman at the Radiumhemmet in Stockholm where specialized techniques for the application of intracavitary radium are employed in the primary therapy. The question to which an answer is being sought currently in many gynecologic clinics is whether the preoperative addition of radium and/or x-ray therapy will materially increase the survival rates in operable cases. Some investigators seem to feel that this question has long since been settled in favor of preliminary irradiation, but it should be noted that the surgical results used for comparisons often antedate the irradiated material by many years. The two sets of data, then, are not exactly suitable for comparison since many extraneous factors may have influenced the final results. It seems unlikely that this question will be settled until alternation of hysterectomy with and without preceding irradiation has been carried out in sufficient numbers of patients to warrant statistical analysis of the results.

The experience reviewed here leads to a number of apparent conclusions, some of which have already been mentioned in describing the results. The poor results obtained in the group treated with a single radium applicator in the uterine cavity, with or without the addition of deep x-ray, strongly suggest that this is an incomplete form of treatment. Whenever possible, total hysterectomy should follow irradiation. Operability cannot be determined routinely on the basis of bimanual pelvic palpation.

While the virtues of standardized treatment for various types of malignant tumors are now generally recognized, this study demonstrates the difficulties which arise when an attempt is made to subject a large number of elderly women to a standard therapeutic plan. It was found, for example, that only 53 per cent of the patients received "routine" treatment, and that only 71 per cent were adequately treated in the sense that hysterectomy was performed. The salvage in the group which could not be hysterectomized will, after five years, be extremely small. Many of these were beyond real help when first seen. While it appears that 100 per cent of those receiving routine therapy might ideally be expected to survive, accidental deaths within this group will inevitably reduce the final figure by 10 or 20 percentage points. The final survival or cure rates, then, can be estimated fairly well in advance from the nature of the treatment which it has been possible to provide. This is shown particularly well in the small group given deep x-ray therapy from 1939 to 1941. Approximately 60 per cent went through the full therapeutic program, and approximately 60 per cent have survived for three to four and one-half years. The five-year figure may be expected to be somewhat below the percentage of patients subjected to full therapy.

The immediate undesirable effects of giving full-tolerance doses of x-ray to patients with carcinoma of the uterine corpus suggest that persistence with

this part of the therapy will add little or nothing to the ultimate cure rates. Certainly in this small series the primary mortality attributable to irradiation was excessive (8 per cent), and the morbidity likewise was great. One gets the impression that the acute complications of irradiation therapy are comparatively enormous in elderly women of poor general physical status, many of whom are obese, and it should be emphasized that the patients in question here were hospitalized throughout the course of x-ray treatments and were given extraordinary attention with a view to minimizing complications. When it became obvious that the morbidity and mortality were abnormally high in this group of patients, we no longer felt justified in continuing preoperative deep x-ray as a part of the routine treatment. It should be noted, however, that this has not been the experience in certain other clinics, but it is difficult to determine from the literature whether comparable amounts of x-ray therapy were administered over similar periods of time.

It is, of course, too early to evaluate the results of treatment with radium and hysterectomy in patients seen since July, 1941, but it may be said that the trend in survival rates is reasonably favorable up to the present time. There continues to be approximately a 30 per cent loss in the first full year after the year of treatment, inasmuch as this share of the total group represents patients whose prognosis is virtually hopeless from the beginning.

Nothing is to be gained, particularly, by comparing the results of treatment in the series reported here with results previously recorded in the literature. For reports of five-year cure rates ranging from 38 to 74 per cent the reader is referred to the papers of Healy and Brown, Miller, Masson and Gregg, Ward, Watkins and Neilson, and Scheffey et al. The recent report of Schmitz and his co-workers describes the effects of high voltage x-radiation (800 kv.) on the uterus containing adenocarcinoma, but the patients so treated had been followed for only short periods of time.

Summary and Conclusions

The results of treatment in the University of Minnesota Hospital of 225 patients with adenocarcinoma of the uterine corpus have been reviewed. One hundred and eleven of these were seen more than five years ago. No patient has been lost in the follow-up program.

The absolute five-year cure rate has been 45 per cent, including certain patients previously treated elsewhere. The exclusion of these latter patients does not improve the end results.

Poor results are shown to follow routine use of radium and x-ray alone. Certain patients so treated may be salvaged even many years later by hysterectomy for recurrent or perhaps persistent carcinoma.

Good results have followed the use of total hysterectomy, with or without preoperative or postoperative irradiation.

Since the beginning of 1939, only 53 per cent of the patients have been able to go through a planned, standardized routine of treatment. The reasons which necessitated modifying the standard therapy are shown in detail. Approximately 70 per cent of the patients were given what might be termed adequate treatment, in the sense that total hysterectomy was performed.

In the past five years only one patient out of the group receiving routine or standardized treatment has died of recurrent carcinoma.

The operative mortality for the entire series has been 5.8 per cent uncorrected, or 3 per cent, corrected (see text).

The results in terms of immediate morbidity and mortality in 38 patients given full-tolerance doses of deep x-ray preceding intrauterine radium and hysterectomy were undesirable. It is suggested that preoperative deep x-ray therapy will add nothing to the ultimate cure rates.

No conclusions can as yet be drawn from recent experience with intra-uterine radium followed in four to six weeks by total hysterectomy.

The final results in the treatment of carcinoma of the uterine corpus are predetermined to a considerable extent by the nature of the material presented for therapy, in terms of metastases, medical and surgical complications, age, weight, and nutritional status.

References

- Healy, W. P., and Brown R. L.: *AM. J. OBST. & GYNEC.* 38: 1, 1939.
 Heyman, J., Reuterwall, O., and Benner, S.: *Acta radiol.* 22: 11, 1941.
 Masson, J. C., and Gregg, R. O.: *Surg., Gynec. & Obst.* 70: 1083, 1940.
 Miller, N. G.: *AM. J. OBST. & GYNEC.* 40: 791, 1940.
 Scheffey, L. C., Thudium, W. J., and Farrell, D. M.: *AM. J. OBST. & GYNEC.* 46: 786, 1943.
 Schmitz, H. E., Sheehan, J. F., and Towne, Janet: *AM. J. OBST. & GYNEC.* 45: 377, 1943.
 Stowe, L. M.: To be published in *AM. J. OBST. & GYNEC.*
 Ward, G. G.: *AM. J. OBST. & GYNEC.* 44: 303, 1942.
 Watkins, R. E., and Neilson, D. R.: *West. J. Surg.* 50: 17, 1942.

STUDIES IN AMENORRHEA, OLIGOMENORRHEA, AND ANOVULOMENORRHEA

I. Effect of Equine Gonadotrophin Upon Establishment of Cyclic Menses and Ovulation

A. R. ABARBANEL, A.B., M.D., AND J. H. LEATHEM, A.B., M.A., PH.D.,
 WASHINGTON, D. C.

(From the Department of Obstetrics and Gynecology, George Washington University School of Medicine, Washington, D. C., and the Department of Zoology, Rutgers University, New Brunswick, N. J.)

Introduction

AMONG the many desiderata of gynecic endocrine therapy, has been the evolution of a gonadotrophin which would efficiently stimulate the clinically hypofunctioning ovary. Ever since the anterior pituitary-gonadal inter-relationship was demonstrated conclusively by Zondek and by Smith and Engle, the clinician has been eagerly awaiting the isolation of a truly potent gonadotrophin. Scores of substances have been brought forth to flourish briefly in the flow of clinical enthusiasm only to fade slowly beyond the horizon on the ebb of critical clinical evaluation and then finally be discarded with the stamp "tried but found wanting."

Recently, a gonadotrophin isolated from the serum of the pregnant mare, known as equine gonadotrophin (hereafter designated as E.G.), has been offered to the medical profession. This gonadotrophin has been found to resemble in its activity certain extracts of the anterior hypophysis, particularly in its ability to produce ovulation in the laboratory animal.¹ The clinical usage of E.G. received an enormous impetus in 1938 when Davis and Koff

reported that they *seemingly* had been able to produce ovulation in the human female with this substance.²

Material and Methods

Twenty-two patients were studied. Three had primary amenorrhea, and the remainder secondary amenorrhea, oligomenorrhea, and/or anovulomenorrhea. Each patient was evaluated over a period of three to nine months before any E.G. was administered. Pretreatment data included endometrial biopsies, determinations of the basal metabolic rate, red cell count and hemoglobin, as well as routine urinalysis and, where indicated, x-ray studies of the chest and sella turcica as well as forearm and wrist for bone age. In addition, an attempt was made to have each patient interviewed carefully by a skilled dietitian as to her dietary regime and as to how it was prepared.

If regular menses did not appear after an observation period of three to nine months, adjuvant therapy with equine gonadotrophin was instituted. In some cases, hormone therapy was administered in an effort to produce ovulation in patients who were seemingly not ovulating. The criterion of an ovulatory response was the finding of a secretory endometrium within two to three weeks after therapy. Almost every biopsy was fixed in picric alcohol and stained for glycogen in addition to the routine hematoxylin and eosin stain.

Each course of equine gonadotrophin was usually given over a period of seven to ten days. If 2,000 I.U. were to be administered, the following schedule was ordered: the initial dose of 200 I.U. was followed in two to three days by 400 I.U., then after the same interval by 600 I.U., all intramuscularly. The final dose of 800 I.U. was given intravenously, two to three days later. Occasionally the entire course was given solely by the one or the other route. As a rule, seven to twenty-one days after the last injection of E.G., an endometrial biopsy was secured. In some instances this was purposely omitted.*

Two preparations of E.G. were used. The less purified product was the commercially available one containing 0.0002 mg. of nitrogen per international unit. The other was 2.5 times more highly purified (as regards nitrogen content), containing only 0.00008 mg. per international unit.

Results.—The pertinent data have been presented in Table I, while the results have been summarized in Table II.

Primary Amenorrhea.—Briefly, it was noted that in these three cases, E.G. was without any effect as far as the appearance of menstruation was concerned.

Secondary Amenorrhea.—There were eleven cases of secondary amenorrhea whose duration ranged from four to twenty-six months. In eight of these, equine gonadotrophin proved ineffectual in stimulating either ovulation or the re-establishment of regular menstrual cycles. The remaining two (Cases 10 and 12) apparently did seem to show a transient favorable response to E.G.

In Case 12, endometrial biopsies taken over a period of six months disclosed an early secretory picture on one occasion after an amenorrhea of 5.5 months. Two subsequent biopsies showed a late proliferative phase premenstrually. She failed to menstruate for two months. Accordingly, she was given 4,000 I.U. equine gonadotrophin. Twenty-six days later she began to experience what seemed to be menstrual cramps. She was given 400 I.U. that day, and a week later an endometrial biopsy disclosed a premenstrual secretory phase. However, no menses occurred the following month. At this time, she went to live and work on a farm. Soon thereafter, menses reappeared and then recurred at regular intervals. This good result was most plausibly caused by the adoption of an adequate diet.

The other patient with secondary amenorrhea (Case 10) seemingly ovulated following equine gonadotrophin. This result, however, is open to serious question, because ovulation apparently did not occur in response to E.G. *before* she received thyroid extract, but only *after* she had been on it for three months. Since thyroid extract alone could accomplish the same effect, and did in several other cases, the ovulatory effect cannot indubitably be attributed to the equine gonadotrophin.

Oligomenorrhea.—Of the seven cases in this category, six showed no response to E.G. as far as either ovulation or more regular menses was concerned. In one (Case 9) menses did seem to become more regular following one or more courses of equine gonadotrophin. But it must be emphasized that she was on iron and a special diet at the same time. On

*It was often noted that endometrial biopsy was frequently followed by menstruation. As a result, this procedure was purposely omitted in some cases in order to note whether menses would occur spontaneously.

TABLE 1

CASE NO.	AGE	MENST. & OBST. HISTORY	PRESENT ILLNESS	B.M.R.	R.B.C.	HGB. (%)
1	17	none	primary amen.	+ 4	5.94	80
2	19	none	primary amen.	- 4	4.07	65
3	16	none	primary amen.	-16	4.46	70
4	39	14 × 30 × 4 grav. 0	amen. 7 mo.	+ 3	4.84	85
5	28	15 × 30 × 5 grav. 0	amen. 7 mo.	+13	3.80	65
6	26	12 × 28 × 3 grav. i para i	amen. 2 yr.	-12	3.98	70
7	24	13 × 30 × 4 grav. 0	amen. 5 mo.	+ 7	4.20	80
8	27	16 × 30 × 4 grav. 0	amen. 4 mo. wt. gain 92 lb. in 2 yr. now 242 lb.	+13	3.80	65
9	36	12 × 28 × 7 grav. i para 0	amen. 26 mo.	-10	4.36	78
10	24	12 × 28 × 4 grav. iv para iv	amen. 14 mo.	-13	4.20	80
11	19	13 × 28 × 4 grav. 0	amen. 9 mo.	- 6	4.38	86
12	35	12 × 28 × 4 grav. 0	amen. 5 mo.	- 4	3.40	70
13	18	12 × 28 × 4 grav. i para i	amen. 2 yr.	- 1	5.56	65
14	26	12 × 28 × 3 grav. i para i	amen. 2 yr.	-12	3.98	70
15	36	13 × 30 × 4 grav. 0	menses q. 4-6 mo. for 4 yr.	- 8	3.35	67
16	27	13 × 30 × 5 grav. 0	menses q. 2-4 mo. for 2 yr.	-15	3.38	67
17	24	14 × 30 × 4 grav. 0	menses q. 2-4 mo. for 3 yr. wt. gain 70 lb. now 220 lb.	- 9	4.06	78
18	23	14 × 30 × 3 grav. i para i	menses q. 2-8 mo. for 5 yr.	- 4	4.24	60
19	34	14 × 30 × 2 grav. 0	menses q. 2-4 mo. for 3 yr. wt. 232 lb.	- 1	3.56	65
20	23	12 × 30 × 4 grav. 0	menses q. 2-6 mo. for 2 yr.	+ 4	4.86	82
21	27	13 × 30 = 90x 7-10 grav. 0	1 preg., pro- fuse menses	-19	4.40	76
22	23	13 × 28 × 5 grav. 0	sterile 3 yr.	- 5	4.80	82

*E.P. — Early proliferative.
 L.P. — Late proliferative.
 E.S. — Early secretory.
 S. — Secretory, premenstrual.
 E.H. — Endometrial hyperplasia.

ENDOMET. BIOPSY*	PRETREAT- MENT OB- SERVATION (MONTHS)	EQUINE GONADOTROPHIN (I.U.)	ENDOMET. BIOPSY*	FOLLOW-UP AND COMMENT
none	3	4,000		Still no menses 3 mo. later
		4,000		
none	3	4,000		Still amen. 4 mo. later
		4,000		
none	3	4,000		Still amen. 6 mo. later
		4,000		
E.P.	3	4,000		Still no menses 7 mo. later when
		1,000	E.P.	occas. flushes noted
L.P.	3	2,000		No menses in next 3 mo.
E.P.	3	4,000	E.P.	Still amen. 4 mo. later
E.P.		4,000	E.P.	
		2,000	E.P.	
L.P.	8	4,000	E.H.	Still amen. 5 mo. later
L.P.				
S.				
L.P.				
E.P.	6	2,000	L.P.	Still amen. 2 mo. later
E.P.	9	4,000	E.P.	Still amen. 4 mo. later
		4,000	E.P.	
	2	800	L.P.	Secretory phase only after pa-
		400		tient on thyroid for 3 mo.
		800		
E.H.	4	1,200	S.	No menses for 2 mo. Later, reg-
L.P.			E.H.	ular menses with thyroid
E.S.	7	4,000		Remained amen. until diet regu-
L.P.		400	S.	lated
L.P.				
	5	4,000		Still amen. 3 mo. later; lactation
		4,000		"atrophy" of uterus?
E.P.	3	4,000	E.P.	Still amen. 4 mo. later
E.P.		4,000	E.P.	
		4,000	E.P.	
E.P.	5	2,000	L.P.	Still amen. 6 mo. later
E.P.		4,000	L.P.	
E.P.		2,000	L.P.	
E.P.		1,000	E.P.	
E.P.	6	4,000		Still amen. 9 mo. later
E.P.		4,000	E.P.	
E.P.				
E.P.				
L.P.	7	2,000	L.P.	No menses in 2 mo. Later regu-
L.P.				lated on thyroid
S.				
E.P.	4	4,000		No menses for 2 mo.
L.P.		4,000		
E.P.	5	4,000		Menses became more regular (on
L.P.				diet and iron also)
L.P.				
L.P.				
L.P.	6	2,000		Menses still irreg. 3 mo. later
L.P.		1,200	L.P.	
E.P.				
L.P.	6	2,000	L.P.	Menses still irreg. Profuse 6
L.P.		4,000	L.P.	mo. later
		4,000	L.P.	
		6,800	L.P.	
L.P.	6	5,000	L.P.	After thyroid for 7 mo. began to
L.P.				ovulate

TABLE II. SUMMARY OF EFFECTS OF EQUINE GONADOTROPHIN

CONDITION	NO. OF CASES	STIMULATION OF	
		OVULATION	CYCLIC MENSES
Primary amenorrhea	3	0	0
Secondary amenorrhea	11	2	1
Oligomenorrhea	7	0	1
Regular anovulomenorrhea	1	0	0
Total	22	2	2

the other hand, biopsies after the administration of this gonadotrophin failed to reveal any evidence as regards stimulation of ovulation.

Cyclic Anovulomenorrhea.—The patient with regular anovulomenorrhea (Case 22) did not respond to equine gonadotrophin but eventually did to thyroid extract.

Comment.—It might be mentioned in passing that 9 of these 22 cases were eventually salvaged by means of an adequate, properly balanced, and properly prepared diet alone, or in conjunction with thyroid extract.

Discussion

Review of the clinical literature indicates that the efficiency of equine gonadotrophin in the management of the abnormally or hypofunctioning ovary in the human being has often been viewed in a favorable light. Some observers have been reserved in their conclusions. In contrast, others have reported entirely negative results. (For review of literature, see Davis³ and Erving et al.⁴)

Erving, Sears, and Rock, in a carefully presented and detailed report of treatment of 48 cases of amenorrhea, dysfunctional bleeding, and sterility with equine gonadotrophin, concluded that "equine gonadotrophic hormone has not been shown to stimulate ovulation in women with anovulatory bleeding or amenorrhea nor has it any apparent effect in cases of sterility."⁴ Brewer, Jones, and Skiles⁵ obtained two questionable ovulatory responses to equine gonadotrophin in 24 patients. Vogt and Sexton⁶ obtained no evidence of ovulation in 13 cases. Emge⁷ observed no response in ten cases of secondary amenorrhea. In this respect, it should be noted that the three failures reported by Davis and Koff² were all cases with endometrial hyperplasia. These results are in accord with our findings.

The experimental data of Hartman deserves careful attention. This skillful, experienced, and sagacious observer was able to keep his female monkeys under lock and key and thus carefully supervise them for a long control period. These monkeys exhibit a very high incidence of anovulatory menstrual cycles during the nonbreeding season. Using E.G., Hartman⁸ obtained only 7 instances of apparently successfully ovulations in 104 attempts. In 16 cases, abnormal stimulation was evidenced by overdistention of the follicles, hyperplasia of the granulosa cells, as well as an increased number of large cystic follicles. In line with the latter, some investigators have noted suggestive evidence of increased estrogenic output, presumably from ovarian stimulation, the criterion of which was increased proliferation of the endometrium.⁶ In the human ovary, Greenblatt⁹ and Geist, Gaines, and Salmon¹⁰ noted that some cases exhibited proliferation of the granulosa cells and slight proliferation and occasional luteinization of the theca interna cells, but no instance of ovulation was found which could be indubitably attributed to equine gonadotrophin. In this series, one case showed abnormal stimulation as witnessed by the appearance of cystic glandular hyperplasia after therapy, while a second developed further proliferation of the endometrium. No evidence of ovarian cyst was observed, although such an occurrence has been reported.⁴

As far as stimulation of ovulation is concerned, the gonadotrophic influence of equine gonadotrophin upon the hypofunctioning human ovary still remains to be proved. Moreover, our data indicate that the development of antagonistic substances to E.G. (antigonadotrophins?) does not explain the negative results obtained, because in the groups treated with the more highly purified preparations of E.G., antagonists to E.G. were rarely evoked.¹¹

Comment

Adoption of the viewpoint that these functional disorders of menstruation are in reality local manifestations of a constitutional disturbance seems most nearly to approach the basic facts. Fundamentally, such ovarian dysfunction most frequently reflects disturbances in the metabolism of the individual in general. As a result, there occurs a disruption in the normal metabolic cycle of the endocrine glands themselves, the recipient end organs, or both. Two of the important basic factors essential for the normal metabolic functioning of the intricate human machine are the nutritional intake and its utilization, and the thyroid hormone.

Diet is of fundamental importance because each of us actually represents the sum total of what he eats and drinks and how the body utilizes these substances. For a long time, clinical as well as experimental evidence has been at hand to show that the functional, and eventually the structural, integrity of the reproductive systems is largely dependent upon an adequate and nutritionally balanced diet.¹² Obviously, then, when nutritional insults have been heaped for years upon the body in general, and the reproductive organs in particular, regressive structural changes may take place that in time become irreversible. If such is true, then an explanation is at hand for the failure of several of these cases to respond to diet and thyroid.

The general metabolic stimulus of the thyroid hormone has long been recognized. What has been less generally realized by the clinician is the relationship between the thyroid and the pituitary on one hand and the pituitary-gonadal relationship on the other. From the experimental evidence at hand, thyroid deficiency results in regressive changes in cells of the anterior pituitary. Since the latter in turn secretes the gonadotrophic substances essential for normal functioning of the gonad (production of gametes and internal secretions), regressive changes result in the ovary or testes.¹³ On the other hand, administration of thyroid hormone will result in regranulation of those pituitary cells with restoration of their normal metabolism, including the secretion of gonadotrophins. In short, the thyroid hormone is essential for the normal functioning of the anterior pituitary in producing gonadotrophic hormone(s).¹⁴ In addition, thyroid may also influence the gonad directly through its influence upon cellular metabolism.

In view of these considerations, it certainly seems like more rational therapy to influence the clinically hypofunctioning ovary by means of its normal regulator, the anterior pituitary, through the administration of a nutritionally balanced diet and the thyroid hormone than by the use of substitute heterogeneous gonadotrophins whose value is as yet unproved and whose effects at best are temporary and may even be gonadotoxic.

Our results with thyroid extract both in this study and in other cases clearly reveals that thyroid hormone still remains the endocrine preparation par excellence for the management of functional menstrual disorders. Of the 9 cases in this series which were eventually "salvaged," the successful therapeutic result in 8 was correlated with the use of thyroid, an adequate dietary

regime, or both. It should be emphasized that the basal metabolic rate is only a relative determination to be evaluated in the light of the patient's clinical picture. For example, Case 7 had a basal metabolic rate of +18 on three occasions, checked twice each time. Yet it was not until she was placed on 190 mg. (3 grains) of desiccated thyroid daily that she began to menstruate regularly, and eventually a secretory endometrium was found premenstrually.

From a clinical point of view, the evocation of antagonistic (antigonadotrophic?) substances to *equine gonadotrophin* is of great importance not only in realizing that subsequent therapy with equine gonadotrophin may be useless but also in explaining certain reactions to it. This subject has been discussed more fully in previous papers.¹¹ Allergic manifestations to equine gonadotrophin have been reported by several investigators, including Erving, et al.,⁴ Bickers,¹⁵ and Fluhman.⁷ *These may occur in spite of negative skin tests.*

Summary

Twenty-two patients with clinically hypofunctional ovarian activity were studied. These comprised 3 cases of primary amenorrhea, 11 of secondary amenorrhea, 8 of oligomenorrhea, and one of cyclic anovulomenorrhea. Adjuvant therapy with equine gonatrophin was instituted in these cases.

This hormone failed to establish menstruation in three cases of primary amenorrhea.

Of the 11 cases of secondary amenorrhea, ovulation was apparently stimulated in two although the result in one was open to serious question. Only one patient continued to have regular menses.

In the 7 cases of oligomenorrhea, equine gonadotrophin apparently restored cyclic menses in one but failed to stimulate an ovulatory response in any.

In the one case of regular anovulomenorrhea, equine gonadotrophin was ineffectual.

Nine of these 22 patients were later "salvaged" with an adequate diet and, usually, thyroid extract.

Conclusions

1. Clinically, equine gonadotrophin proved to be a rather ineffectual stimulant to the abnormally functioning or hypofunctioning human ovary as far as the restoration of normal cyclic metabolism and the reappearance of regular menstrual rhythm was concerned.

2. Equine gonadotrophin produced similarly poor results in stimulating an ovulatory response in patients with clinically hypofunctioning or abnormally functioning ovaries.

3. The principle of heterogenous substitutive therapy with equine gonadotrophin may yield far greater harm than any temporary good. The possible harmful results of therapy with equine gonadotrophin are (a) a gonadotoxic effect on the ovary as evidenced by abnormal stimulation or marked delay in appearance of the next menses, (b) development of antagonistic (antigonadotrophic?) substances with neutralization of subsequent injections of equine gonadotrophin, (c) development of allergic manifestations, which may be severe in spite of negative skin tests, (d) sensitization of the patient to other as yet unknown components of horse serum.

4. The principle of physiologic stimulative therapy by means of a nutritionally balanced diet and desiccated thyroid extract is far more rational and far more efficacious both on theoretical considerations and on the clinical results obtained.

The authors are indebted to Dr. H. C. Falk, Director of the Department of Gynecology of Harlem Hospital, for permission to carry out most of this work and to publish our findings.

Both preparations of equine gonadotrophin were supplied as Gonadogen, by Dr. G. F. Cartland of the Upjohn Company.

We are particularly grateful to Miss Sylvia Krause, Dietitian in charge of Special Diets at the Harlem Hospital, for her splendid help and cooperation.

This work was carried out for the main part while one of us (A. R. A.) was associated with the Department of Gynecology, Harlem Hospital, New York. Dr. Leatham's studies were begun while he was associated with the Department of Anatomy, College of Physicians and Surgeons, Columbia University, New York, and were continued at Rutgers University, New Brunswick, New Jersey.

References

1. Cole, H. H., and Hart, G. H.: *Am. J. Physiol.* 93: 57, 1930.
2. Davis, M. E., and Koff, A. K.: *AM. J. OBST. & GYNEC.* 36: 183, 1938.
3. Davis, M. E.: *J. Clin. Endocrinol.* 3: 517, 1943.
4. Erving, H. W., Sears, C., and Rock, J.: *AM. J. OBST. & GYNEC.* 40: 695, 1940.
5. Brewer, J., Jones, H. O., and Skiles, J. H.: *J. A. M. A.* 118: 278, 1942.
6. Vogt, W. H., Jr., and Sexton, D. L.: *AM. J. OBST. & GYNEC.* 48: 81, 1941.
7. Emge, L.: In Discussion of paper by Fluhman: *West. J. Surg.* 48: 63, 1940.
8. Hartman, C. G.: *Bull. Johns Hopkins Hosp.* 63: 351, 1938.
9. Greenblatt, R. B.: *AM. J. OBST. & GYNEC.* 42: 983, 1941.
10. Geist, S. H., Gaines, J. A., and Salmon, V. J.: *AM. J. OBST. & GYNEC.* 42: 619, 1941.
11. a) Leatham, J. H., and Abarbanel, A. R.: *J. Clin. Endocrinol.* 3: 206, 1943.
b) *Ibid.*: *West. J. Surg.* 51: 177, 1943.
12. Mason, K.: In *Sex and Internal Secretions*, ed. 2, Baltimore, 1939, Williams & Wilkins Co., Chap. XXII.
13. Sevringhaus, A. E.: In *Sex and Internal Secretions*, ed. 2, Baltimore, 1939, Williams & Wilkins Co., Chap. XIX.
14. Sevringhaus, A. E.: *West. J. Surg.* 50: 371, 1942.
15. Bickers, W.: *J. Clin. Endocrinol.* 1: 852, 1941.

1726 EYE STREET, N.W.

A COMPARATIVE STUDY OF THE CLINICAL RESPONSES OF WOMEN WITH HYPOFUNCTIONING OVARIES TO TWO METHODS OF COMBINED GONADOTROPIC THERAPY*

C. D. DAVIS, M.D., AND E. C. HAMBLÉN, M.D., DURHAM, N. C.

(From the Endocrine Division of the Department of Obstetrics and Gynecology, Duke University School of Medicine and Duke Hospital)

A RECENT study by us,¹ which included data previously reported by other members of our group, has shown that the sequential and cyclic administration of equine and chorionic gonadotropins (one-two cyclic gonadotropic therapy) restores to a fertile status a significant number of women with hypofunctioning ovaries. The commercial availability of a product† which contains both pituitary synergist and chorionic gonadotropin (called hereafter SYN.) has suggested the likelihood that it may yield as effective therapy as the sequential and separate administration of equine and chorionic gonadotropins.‡ This communication is concerned with a comparative study of the two methods of treatment in a group of twenty-one patients.

*Parts of the expenses of these studies were defrayed by grants to one of us (E.C.H.) by the Research Council of Duke University, and by Parke, Davis and Co., Detroit, Mich.

†Synapoidin, Parke, Davis and Co., Detroit, Mich.

‡Equine gonadotropin: Anteron (Schering Corporation) and Gonadogen (Upjohn Company); chorionic gonadotropin: APL (Ayerst, McKenna and Harrison); and chorionic gonadotropin (Upjohn Company).

Selection of Patients

The twenty-one patients fell into four clinical categories: (1) those with deficient sexual maturation whose menarches had not occurred, four patients; (2) those with infrequent and/or scanty estrogenic bleeding, six patients; (3) those with prolonged and/or excessive estrogenic bleeding, five patients; and (4) those with presumed ovarian sterility associated with bleeding from immature progestational endometriums, six patients.

1. *Patients With Deficient Sexual Maturation Whose Menarches Had Not Occurred.*—All possessed striking hypoeestrogenism. In none a definite diagnosis of hypopituitarism was made. Accordingly, the likelihood of an intrinsically ovarian etiology existed in all. The endocrine state of these patients was not relatable to organic or constitutional disease. Hypothyroidism, as an etiological factor, was eliminated by clinical studies, basal metabolic rates, and by preliminary treatment with desiccated thyroid gland of those patients in whom there was some evidence of hypothyroidism.

2. *Patients With Infrequent and/or Scanty Bleeding.*—Upon the basis of endometrial biopsies secured at the onsets of episodes of uterine bleeding, all of these patients were judged to have anovulatory ovarian failure, that is, they bled from interval or estrogenic endometriums. There was no evidence of hypoeestrogenism.

No more definite statements of the etiology of the ovarian failure for this group of patients were possible than for the first group.

3. *Patients With Prolonged and/or Excessive Bleeding.*—In common with the patients of the second group, these patients were characterized by anovulatory ovarian failure without hypoeestrogenism, that is, all bled from estrogenic or interval endometriums.

Similar to the patients of the first and second groups, no definite diagnoses of the etiology of the ovarian failure were possible; however, constitutional and organic gynecologic factors were excluded.

4. *Patients With Presumed Ovarian Sterility Associated With Bleeding From Immature Progestational Endometriums.*—We assumed that bleeding from immature progestational endometriums by these patients was significant of endocrine deficiency since no other demonstrable causes of sterility were found in careful diagnostic surveys of these wives and their husbands. We considered two likely mechanisms: (1) ovulations might have occurred and, yet, the immature progestational endometriums might have prevented nidation of any fertilized ova, that is, the existence of hypoprogesterinism without anovulatory ovarian failure; and (2) ovulations might not have occurred and, instead, ova were imprisoned in follicles, the granulosa of which subsequently became luteinized providing low progesterin stimulation of the endometrium, that is, the existence of anovulatory ovarian failure and hypoprogesterinism. Acceptance of the latter of these two mechanisms justified the use of gonadotropic therapy.

No more definite causes for the ovarian failure of this group of patients were ascribable than for that of the patients of the third group.

All of the patients of this group experienced cyclic and essentially normal bleeding with regard to duration and amount. Therefore, they stand in striking contrast to the patients of the second and third groups.

Method of Study

The clinical studies of all of the patients embraced endocrine and gynecologic surveys, determinations of basal metabolic rates, and roentgenograms of the sella turcica. Roentgenologic estimations of osseous age were made in those patients with deficient sexual maturation and those 20 years of age or less. Endometrial biopsies were done at the onset of episodes of bleeding, prior to, during, and frequently after therapy. Because of the hypoeestrogenism of the patients of the first group, initial biopsies were omitted. At least two consecutive episodes of bleeding were biopsied, if possible, prior to treatment of the patients of the second, third, and fourth groups. This seemed advisable lest chance variations might be classed as ovarian habits of a patient.

All biopsy material, after fixation, mounting, and staining, was studied and classified by one of us (E.C.H.). This practice has been followed in previous studies and, thereby, has permitted a uniformity and continuity of interpretation of endometrial responses.

Details of the special methods of handling these groups of patients were given in a previous communication.¹ These included use of estrogens for hemostasis (in prolonged and/or excessive bleeding), use of estrogens for sexual maturation (in deficient sexual maturation), use of cyclic estrogen therapy for cycle regulation (patients of first, second,

and third groups), test of endometrial receptivity to progesterone therapy (patients of first, second, and third groups) and salvage test (patients of first, second, and third groups).

Therapeutic Schedules

The schedules for *hemostasis*, *cyclic estrogen therapy*, and for *cyclic estrogen-progesterone therapy* were given in a previous communication.¹

One-Two Cyclic Gonadotropic Therapy.—Prior to initiating one-two cyclic gonadotropic therapy, all patients were skin tested with the equine gonadotropin preparation to ascertain possible allergy. Skin tests were repeated before each projected series of therapy. Patients with definite allergy were not treated.

Gonadotropins were given intramuscularly and daily. Therapy was initiated on the fifth day of the cycle. From the fifth through the fourteenth days of the cycle, patients received intramuscularly and daily 400 international units of equine gonadotropin. From the fifteenth through the twenty-fourth days of the cycle, patients received intramuscularly and daily 500 international units of chorionic gonadotropin. When bleeding occurred before treatment was completed, injections were discontinued.

As a rule, and out of respect for possible antibody or antihormonal phenomena, series of one-two cyclic gonadotropic therapy were not given in sequence but, instead, several months were allowed to elapse between any two series of therapy.

SYN. Therapy.—Two schedules employing the preparation of pituitary synergist and chorionic gonadotropin were used: (1) 10 SYN., and (2) 20 SYN.

10 SYN. embraced the daily and intramuscular administration of 30 "synergy units" of SYN. from the fifth through the fourteenth days of the cycle.

20 SYN. embraced the daily intramuscular administration of 30 "synergy units" of SYN. from the fifth through the twenty-fourth days of the cycle.

Patients were skin tested with SYN. prior to each series of therapy in order to avoid allergic phenomena.

Clinical Data and Results

1. *Patients With Deficient Sexual Maturation Whose Menarches Had Not Occurred.*—The ages of these four patients ranged from 16 to 19 years.

Three of the four patients received a total of four series of 10 SYN. therapy. All yielded hypoestrogenic or atrophic endometria at the onsets of bleeding which followed therapy.

Three of the four patients received a total of four series of 20 SYN. therapy. All yielded hypoestrogenic or atrophic endometria at the onsets of bleeding which followed therapy.

The four patients received a total of five series of one-two cyclic gonadotropic therapy. All patients yielded hypoestrogenic or atrophic endometria at the conclusion of therapy.

2. *Patients With Infrequent and/or Scanty Bleeding.*—The ages of these six patients ranged from 17 to 35 years. Their menarcheal ages ranged from 11 to 15 years.

Two were single and four married. Two of the married patients were nulliparous, one had had twins, and one an abortion.

When first seen, the elapsed time between the last bleedings of these patients varied from three to thirteen months.

Two of the six patients received a series of 10 SYN. therapy. Both patients yielded estrogenic endometria at bleeding following the conclusion of therapy (one normal estrogenic and one hypoestrogenic endometrium).

Five of the six patients received a total of six series of 20 SYN. therapy. Four patients yielded estrogenic endometria (two normal estrogenic and two hypoestrogenic) after their therapy. The fifth patient, who was given two series of therapy, yielded an immature progestational and normal estrogenic endometrium.

All six patients received one-two cyclic gonadotropin therapy. A total of seven series was given. The patient who gave an immature progestational response to 20 SYN. therapy yielded a full-blown progestational endometrium after one-two cyclic gonadotropic therapy. The other five patients yielded three normal estrogenic and three hypoestrogenic endometria after therapy.

3. *Patients With Prolonged and/or Excessive Bleeding.*—The ages of the five patients ranged from 16 to 31 years. Their menarcheal ages ranged from 12 to 15 years.

Three of these patients were single and two married. One of the married patients was nulliparous and one had had an abortion.

Four of the five patients when first seen had had episodes of prolonged bleeding which ranged from twenty-three days to twenty months in duration. One had had excessive bleeding of six days in duration. The severity of the uterine hemorrhages of these patients is indicated by their hemoglobin values, which ranged from 45 to 81 per cent, with an average value of 61 per cent.

Three of these patients received a total of three series of 10 SYN. therapy. Following therapy, two patients gave normal estrogenic endometriums and one a hypoenestrogenic endometrium.

All five patients received 20 SYN. therapy for a total of five series. Two patients gave progestational endometriums at the conclusion of therapy: one full-blown progestational endometrium and one immature progestational endometrium. The other three yielded normal estrogenic endometriums at the end of therapy.

All five patients received one-two cyclic gonadotropic therapy for a total of five series. Four of the five patients yielded full-blown progestational endometriums and one a normal estrogenic endometrium at the conclusion of treatment. Both of the patients who gave positive responses to 20 SYN. therapy yielded progestational responses following one-two cyclic gonadotropic therapy.

4. *Patients With Presumed Ovarian Sterility Associated With Bleeding From Immature Progestational Endometriums.*—The ages of these six patients ranged from 23 to 29 years. Their menarcheal ages ranged from 11 to 16 years.

All were married: five were nulliparous and one had had one term delivery.

The bleeding of these patients was cyclic and of normal amount and duration.

Five of the six patients received 10 SYN. therapy, one series to a patient. Three patients gave immature progestational endometriums following treatment, one a full-blown progestational endometrium, and one supplied insufficient endometrium for diagnosis.

One of the six patients received 20 SYN. therapy. Following therapy, a full-blown progestational endometrium was found.

Three of the six patients were treated with one-two cyclic gonadotropic therapy, one series to a patient. Two yielded immature progestational endometriums following therapy and one a full-blown progestational endometrium.

None of these six patients became pregnant in relation to SYN. or one-two cyclic gonadotropic therapy.

Discussion

The initial clinical report on the experimental use of SYN. by Mazer and Ravetz² established its gonadotropic properties. Following intensive therapy prior to laparotomy, these observers found multiple corpora lutea together with evidences of overstimulation in the ovaries of twenty out of twenty-three women who were treated. Two facts stood out from this study: (1) their patients apparently were characterized by normally reactive ovaries and their responses were augmentational ones typified by multiple corpora lutea; (2) the apparent overstimulation observed in these ovaries aroused the questions as to whether or not physiologically normal ova were discharged and whether or not normally functioning corpora lutea resulted.

Subsequently other clinical studies employing SYN. appeared.³⁻⁵ These included ovarian studies after preoperative administration of SYN. and studies which described applications to the treatment of hypoovarian states. None of these studies has established any definite therapeutic application of SYN.

Our selection of dosage schedule was based fundamentally on arbitrary grounds. In a previous report⁶ of our results with SYN. in the treatment of males with seminal inadequacy, we encountered disagreeable constitutional and local reactions when relatively large doses of SYN. were used. Accordingly, we chose a daily dose of 30 "synergy units" (or 2 c.c. of the commercial preparation). This amount appeared to be about all that the average patient could tolerate without too frequent untoward reactions.

Two therapeutic schedules employing SYN. were used. One of these emphasized the follicle-stimulating possibilities of SYN., embracing its adminis-

tration from the fifth through the fourteenth days of the cycle. The other schedule took into account probable follicle-stimulating and luteinizing functions of SYN., being characterized by its administration from the fifth through the twenty-fourth days of the cycle.

Despite the fact that no patient was treated with SYN. who gave a positive skin test prior to a series of anticipated therapy—and, incidentally, a number of patients who otherwise might have been treated with this preparation were disqualified on these grounds—three of the twenty-one patients experienced rather severe local and constitutional reactions. One patient on the thirteenth and fourteenth days of therapy experienced severe systemic reaction, characterized by fever, general malaise, and impossibility of moving the arm because of pain. Therapy was promptly discontinued. Endometrial biopsy subsequently yielded a full-blown progestational endometrium. Another patient on the seventh day of therapy had a moderately severe general systemic reaction. A third patient required discontinuation of treatment on the tenth day because of severe local reaction at the site of injection. These reactions to SYN. should be contrasted with the infrequency of reactions during one-two cyclic gonadotropic therapy.¹

The endometrial responses to SYN. and one-two cyclic gonadotropic therapy of the patients with deficient sexual maturation were essentially the same. No patient gave any evidence that her ovaries were stimulated to full physiologic activity. These findings are in line with those reported in a larger series of similar patients treated with one-two cyclic gonadotropic therapy.¹

The endometrial responses of the patients with infrequent and/or scanty bleeding to both forms of treatment were in fairly good agreement. Only one of the six patients responded to gonadotropic therapy and she responded to both 20 SYN. and one-two cyclic gonadotropic therapy. A full-blown progestational endometrium followed one-two cyclic gonadotropic therapy, whereas an immature progestational endometrium followed 20 SYN. therapy.

The endometrial responses of the five patients with prolonged and/or excessive uterine bleeding are consistent. Two of the patients who received 20 SYN. therapy yielded progestational endometria, one giving a full-blown and one an immature progestational response. These same two patients also responded to one-two cyclic gonadotropic therapy, both giving full-blown progestational responses. Two other patients who failed to respond to SYN. therapy gave full-blown progestational responses to one-two cyclic gonadotropic therapy.

The results of the treatment of six patients with presumed ovarian sterility in association with bleeding from immature progestational endometria were essentially the same for both systems of gonadotropic therapy. In no instance did the therapy reverse the endometrial pattern from a progestational to an estrogenic type. In one of four patients treated with 10 SYN. therapy, the endometrium was advanced to a full-blown progestational type. In the one patient treated with 20 SYN. therapy, the endometrium was advanced to a full-blown progestational status. In one of the three patients treated with one-two cyclic gonadotropic therapy, the endometrium was advanced to a full-blown progestational type. Since no pregnancies have occurred during SYN. therapy, a definite statement cannot be made that physiologically normal responses are elicited in the ovaries. We are of the opinion, however, that when a larger series of patients with sterility is treated with SYN., pregnancies may be obtained.

The data secured from the treatment of patients with infrequent and/or scanty bleeding and with prolonged and/or excessive bleeding indicate that the effective method of administering SYN. is the 20 SYN. therapy schedule, that is, its administration from the fifth through the twenty-fourth days of the cycle. Apparently, dosage increases are not necessary. These would produce, probably, more serious responses. It is apparent, however, that when these two groups of patients are considered, the use of SYN. therapy, although producing favorable responses, does not afford as high an incidence of these responses as the single and sequential administration of equine and chorionic gonadotropins.

Summary and Conclusion

The clinical responses of twenty-one patients (four with deficient sexual maturation, six with infrequent and/or scanty estrogenic bleeding, five with prolonged and/or excessive estrogenic uterine bleeding, and six with presumed ovarian sterility associated with bleeding from immature progestational endometrium) to two systems of gonadotropic therapy were subjected to comparative study. The primary criterion for an evaluation of these responses was a study of endometrial biopsies taken prior to and following treatment. One method of therapy employed the single and sequential administration of equine and chorionic gonadotropins—so-called one-two cyclic gonadotropic therapy. The other method of therapy employed a preparation which contained a mixture of "pituitary synergist" and chorionic gonadotropin. Positive responses followed the latter therapy only when it was given for twenty days, from the fifth through the twenty-fourth days of the cycle.

None of the patients with deficient sexual maturation responded to either therapy. Patients with infrequent and/or scanty estrogenic bleeding and those with prolonged and/or excessive estrogenic bleeding responded to both therapies. More positive responses, however, were associated with one-two cyclic gonadotropic therapy. No pregnancies were associated with either therapy in the group of patients with presumed ovarian sterility associated with bleeding from immature progestational endometriums.

These conclusions appear warranted:

1. Cyclic therapy with a preparation containing "pituitary synergist" and chorionic gonadotropin (30 "synergy units" intramuscularly and daily from the fifth through the twenty-fourth days of the cycle) may produce progestational endometriums in patients experiencing various grades of estrogenic bleeding.

2. This therapy, however, yields a lower incidence of positive responses than so-called one-two cyclic gonadotropic therapy, which employs singly and sequentially equine and chorionic gonadotropins, but a higher incidence of untoward reactions.

References

1. Hamblen, E. C., and Davis, C. D.: *AM. J. OBST. & GYNEC.* 50: 137, 1945.
2. Mazer, C., and Ravetz, E.: *AM. J. OBST. & GYNEC.* 41: 474, 1941.
3. Greenblatt, R. B.: *AM. J. OBST. & GYNEC.* 42: 983, 1941.
4. Greenblatt, R. B., and Pund, E. R.: *South. M. J.* 34: 730, 1941.
5. Gray, L. A.: *AM. J. OBST. & GYNEC.* 43: 387, 1942.
6. Davis, C. D., Madden, J. H. M., and Hamblen, E. C.: *J. Clin. Endocrinol.* 3: 357, 1943.

CARCINOMA OF THE CERVIX COMPLICATED BY PREGNANCY

J. ROBERT WILLSON, M.S., M.D., CHICAGO, ILL.

(From the Department of Obstetrics and Gynecology of the University of Chicago and the Chicago Lying-in Hospital)

BECAUSE carcinoma of the cervix is rare in pregnancy, it usually is not considered in the differential diagnosis of bleeding, and the lesion may not be discovered until it has progressed to a stage at which all hope for a cure is lost. The diagnosis of carcinoma should present no difficulty if the possibility of its existence occurs to the physician. Examination, which must of necessity include visualization of the cervix, is of utmost importance; the final conclusive proof, however, depends upon the microscopic examination of tissue removed from the suspicious area on the cervix.

Danforth,¹ from a series of published reports, concluded that the incidence of cervical carcinoma complicating pregnancy is only 0.0321 per cent. This low figure is not surprising when one considers that the incidence of cancer of the cervix in the nonpregnant is also low in the younger age groups into which most of the childbearing women fall; thus malignancy and pregnancy combined are limited to only a small group of those who are potential candidates for either condition.

Since 1931, six patients with carcinoma of the cervix and pregnancy have been treated at the Chicago Lying-in Hospital (Tables I and II). Of these, two were referred to the hospital for treatment after the diagnosis had been made elsewhere. The remaining four lesions were discovered among our own patients. During this same period of time a total of 39,719 patients have been delivered; thus the incidence of cervical carcinoma in our patients is one in each 6,620 deliveries or 0.015 per cent. All the lesions were of squamous-cell origin with the exception of that in Patient 3, which was adenocarcinoma.

Diagnosis

The diagnosis of early carcinoma of the cervix during pregnancy can be made only if the possibility of its existence is considered. Bleeding which appears during early pregnancy and which persists for more than one week despite bed rest may be due to a malignancy. In such cases it is imperative that a pelvic examination be made (1) to establish the diagnosis of pregnancy, and (2) to determine the cause of the bleeding. In most instances, bloody discharge during the first trimester of pregnancy is due to threatened abortion. In the majority of these cases, however, the bleeding will either stop after a few days' rest in bed or the products of conception will be expelled from the uterus. Abortion usually is accompanied by cramps due to uterine contraction. While examination may hasten or even precipitate the emptying of the uterus in such a case, prolonged observation of pregnant patients who are bleeding from an undetermined site is dangerous. Sterile vaginal examination after one week of bleeding which continues despite complete bed rest is a necessity. The history of a missed menstrual period, severe pain, and bleeding, which usually characterizes an extrauterine pregnancy, calls for a complete and immediate investigation.

TABLE I

PATIENT	DURATION OF PREGNANCY (WEEKS)	SIGNS OF CARCINOMA AND DURATION	SIZE OF LESION AND CLINICAL CLASSIFICATION (SCHMITZ) AT FIRST EXAMINATION	INTERVAL FROM FIRST SIGN TO FIRST TREATMENT
1. Age 39 Para iii	28	No signs. Suspicious lesion found on speculum examination	Small. Confined to posterior lip II	6 days. No delay
2. Age 30 Para v	2½ months postpartum	Painless irregular bleeding 12 months	Entire vaginal vault replaced by neoplasm IV	12 months. Patient did not report to her doctor until late in pregnancy—was not examined
3. Age 42 Para xi	28	No signs. Suspicious lesion found on speculum examination	Entire anterior lip indurated and neoplastic II	27 days
4. Age 32 Para v	38	Postcoital bleeding	Posterior cervical lip indurated and neoplastic II	4 months. Examination for postcoital bleeding revealed no cervical lesion. Biopsy at delivery revealed only "squamous metaplasia"—not taken from area of cancer
5. Age 27 Para iv	6 weeks postpartum	Painless bleeding 6 weeks	Lesion involving both cervical lips II	Refused treatment
6. Age 38 Para viii	28	Painless bleeding 6 months	Entire anterior lip involved. Two nodules invescovaginal septum IV	6 months. Patient did not report for examination

There are no subjective symptoms in the early case of carcinoma of the cervix. The signs during pregnancy are exactly like those which characterize the same lesion in the nonpregnant uterus: abnormal discharge or bleeding which, characteristically, is painless, irregular, progressive in amount, and prone to follow trauma. Pain, weight loss, and palpable extension, all appear late in the course of the disease and need not be considered in diagnosing the early lesion.

The pelvic examination to determine the cause of persistent bleeding must be carried out in a systematic manner. The external genitalia are first inspected and palpated, following which a careful digital exploration of the vagina is made. Early malignant areas on the cervix are characterized by induration or irregularity, which can sometimes be more readily felt than seen. After the entire cervix has been carefully palpated and the diagnosis of pregnancy confirmed, the vagina and cervix must be visualized through a speculum. This is one of the most important steps in the entire examination. Any suspicious area of induration or any cervical lesion which bleeds may be malignant and demands more complete investigation. The diagnosis of carcinoma must be made or at least confirmed by microscopic examination of adequate amounts of tissue taken from the suspected area. Such biopsies may be taken either in the outpatient with a suitable punch, or by excision in the hospital. Only in this way will the presence of an early malignancy be discovered.

It is a generally accepted rule that bleeding in late pregnancy should be

investigated in an effort to rule out placenta previa or abruptio placentae as a cause; at the time of the sterile vaginal examination, the practice of visualization of the cervix is a routine. Adequate biopsy of suspicious cervical lesions, especially of the site of the bleeding, may reveal an unsuspected malignancy. Patient 5 (Table I) was admitted to the hospital at thirty-four weeks' gestation, complaining of profuse painless vaginal bleeding. The placental edge was palpated and an intraovular bag inserted. There was no unusual bleeding during the hospitalization but after discharge the patient noted daily spotting. At the first return visit both cervical lips were involved in a malignant lesion which probably was present at the time of delivery. Had this patient not had a placenta previa as an obvious cause of bleeding, the malignancy probably would have been discovered when the examination was made.

The importance of an accurate pathologic diagnosis on the tissue removed cannot be overemphasized. Not uncommonly, cervicitis or areas of decidual reaction on the cervix during pregnancy may be everted, friable, and bleed freely upon manipulation. Grossly, such lesions cannot be differentiated from carcinoma. The microscopic changes in the pregnant cervix may likewise suggest that a malignant change has occurred. Hofbauer² described a marked proliferation and hyperplasia of the cervical epithelium during pregnancy, characterized by downgrowth of masses of epithelial cells beneath a normal layer of columnar epithelium, into the gland lumina, or beneath normal squamous epithelium. There may be noted a distinct variation in size and shape of the individual cells, mitotic figures, and vacuolization in the newly formed masses. In the cases in which the downgrowth is marked, difficulty may be encountered in differentiating these normal changes from malignancy. The important features of the normal proliferation which distinguish it from carcinoma are: the regularity of the mitoses, the minor changes in size and shape of cells, and the consistently intact basement membrane. If the lesion is found to be benign, it should not be treated during pregnancy. Such changes are part of the normal course of events and cannot be healed until the pregnancy terminates, after which reversion is in most cases spontaneous. Overly enthusiastic treatment of this common lesion might result in scarring and abnormal dilatation of the cervix in labor.

If the microscopic diagnosis is questionable, the patient should not be subjected to intense irradiation therapy which may destroy the fetus and permanently injure the mother. Before the initiation of treatment in such a case, examination of the sections by several competent gynecologic pathologists is essential.

The following two cases, one treated for carcinoma and one observed, illustrate this point:

CASE 1.—C. S., aged 24 years, gravida ii, para i. This patient was first seen in our clinic in February, 1932. At that examination there was noted eversion of the cervix and papillary outgrowths on both lips. Because of a microscopic diagnosis of adenocarcinoma, a plaque containing 200 mg. of radium was applied against the cervix for a total dosage of 3,800 mg. hours, and seven weeks later a cesarean section and modified Wertheim hysterectomy were done. Several competent gynecologic pathologists who examined the sections were all of the opinion that the lesion was not malignant.

Although the patient is still alive and apparently well, she developed a moderate irradiation proctitis, much pelvic pain, was completely castrated, and was subjected to an operative procedure with a mortality rate of 14 per cent, all for the treatment of a benign cervical lesion.

TABLE II

PATIENT	DURATION OF PREGNANCY AT TIME OF DIAGNOSIS	INITIAL THERAPY	METHOD OF TERMINATING PREGNANCY	TREATMENT FOR CARCINOMA			COMPLICATIONS OF TREATMENT	SURVIVAL
				SURGERY	X-RAY DEPTH DOSE TO EACH PARAMETRIUM	RADIUM (MG. HR.)		
1. 188041	28 weeks	Radium in canal and to surface	Cesarean section 2 weeks after radium	Total hysterectomy, bilateral salpingo-oophorectomy	4630 r. 2 series	3000 before delivery	None	Alive 80 months
2. 223781	2½ months postpartum	Radium	Vaginal—without treatment	None	2700 r.	5126 after delivery	None	Dead 14 months
3. 63977	28 weeks	Radium to surface and in canal	Spontaneous delivery 2 weeks after radium	None	4200 r. (skin) Aug., 1932, 4900 r. (skin) Feb., 1937	3100	None	Dead 89 months
4. 151145	38 weeks	Radium	Spontaneous vaginal delivery	None	3200 r.	4900 after delivery	Irradiation proctitis	Alive 23 months
5. 92943	6 weeks postpartum		Vaginal—bag induction for placenta previa	None	None	None		Dead 20 months
6. 32686	28 weeks	Radium to vagina and cervix	Cesarean hysterectomy 6 weeks after radium	None	3000 r.	Cervix 3540. Vagina (internal) 1882 before delivery	None	Alive 10 months

CASE 2.—T. T., aged 33 years, gravida i, para 0. At the time of the initial examination on July 8, 1935, when the patient was about fourteen weeks pregnant, the cervix was described as showing "decidual reaction." On Oct. 21, 1938, slight vaginal bleeding occurred, and a benign cervical polyp was removed. There was no further bleeding until Feb. 8, 1939, at which time the patient was forty-one weeks pregnant. There was noted a friable everted lesion on the cervix which grossly was suggestive of malignancy. Because of an advancing pre-eclampsia, the pregnancy was terminated on Feb. 10, 1939 (forty-one weeks), by laparotrachelotomy which was preceded by a cervical biopsy. The tissue removed was reported to be adenocarcinoma; however, after the sections were reviewed by several members of our staff, it was decided that the lesion was benign. Without treatment the cervix healed and has been normal since. Had the original diagnosis of carcinoma been accepted without question, this patient would undoubtedly have been subjected to a course of irradiation which would have been followed by castration and possibly injury to normal structures.

In another case (No. 4, Table I) delay in treating a carcinoma resulted from an inadequate biopsy. This patient had complained of postcoital bleeding on her first visit to one of our outlying clinics but no cervical lesion was noted on examination. She was admitted to the hospital at thirty-eight weeks' gestation with painless vaginal bleeding. At the time of examination an indurated area noted in the posterior cervical lip was biopsied. The initial report was "squamous metaplasia" and it was not until the second postpartum visit that tissue showing carcinoma was submitted to the pathologist. Thus, the initiation of treatment was delayed by several weeks.

Prognosis

The prognosis for carcinoma of the cervix discovered during pregnancy and properly treated seems to be at least as good as that in the nonpregnant individual; five of Emge's⁴ six cases and three of the four cases reported by Richman and Goodfriend⁵ survived more than five years (of the latter group, one for six years, one for eight years, and the third for five years; the last, however, had extensive involvement at that time). Maino and Mussey⁶ reported 30 per cent five-year survival in twenty patients treated at the Mayo Clinic.

The five-year survival rate for the cases presented here is 50 per cent for those who are eligible for that consideration. Since one of these four patients refused treatment, two, or 67 per cent of those treated, lived more than five years after the initiation of therapy.

This survival rate is not surprising since usually the diagnosis should be made early in the course of the disease. A far-advanced cervical lesion with a large infected fungating tumor mass will, in most instances, preclude conception, but an early lesion may not. The latter type should be discovered at the time of the initial prenatal visit if a complete examination is made.

Two patients in our series (Nos. 1 and 3, Table I) had no symptoms referable to the carcinoma; both were discovered at the time of the initial pelvic examination and one (No. 1) had the smallest lesion found. The other lesion was an adenocarcinoma, in which usually the first sign may be somewhat delayed. This lesion involved only the anterior lip. The first patient is alive and well without evidence of malignancy after six years, and the second survived almost seven and one-half years but died of carcinoma (Table II). The latter was undertreated according to our present knowledge of the amount of irradiation necessary to eradicate carcinoma.

If the tumor appears during the course of the pregnancy, the physician usually is warned by the appearance either of an abnormal discharge or of bleeding which typically is painless, irregular, progressive in amount, and prone to follow trauma. The presence of vaginal bleeding or discharge demands a complete pelvic examination to establish the cause.

The belief that the rate of growth of carcinoma of the cervix is increased

by the pregnancy has not been substantiated. Peller,³ after demonstrating that the relative number of carcinomas occurring during pregnancy was significantly less than the number occurring in similar age groups in the nonpregnant, concluded that pregnancy not only increases the resistance to cancer, but raises the average age of its occurrence and retards its progress.

In addition to the belief that the increased blood and lymph circulation increases the opportunities for spread of the malignancy, it has been suggested that the marked rise in the estrogenic hormones during pregnancy may be a factor both in the production and extension of the disease. This latter supposition is based upon the fact that cancer may be produced in certain susceptible laboratory animals by stimulation with large dosages of estrogens. Emge,⁴ studying rats which were particularly free from breast and genital cancer, carried them through a series of rapidly recurring pregnancies in an effort to produce the maximum stimulation of breast and genital tissue. No malignancies developed in the group of animals and he concluded that the role of the estrogenic hormones in the production of cancer is secondary to, and limited by, the hereditary factors.

The prognosis for those patients who have had no prenatal care or in whom the warning signs have been ignored may be less favorable. Patient 2 in this series (Table II) had had symptoms for twelve months before we first saw her two and one-half months post partum. Although irregular bleeding was noted early in pregnancy and continued throughout, this cardinal sign was ignored both by patient and physician. The former delayed several months in visiting her doctor, and the latter likewise wasted time by treating the bleeding "conservatively" without examination. Eradication of the neoplasm, which when diagnosed almost filled the pelvis, was impossible, and the patient survived only fourteen months after treatment which might have completely destroyed a smaller lesion. Since the advanced lesions usually are grossly infected and the carcinomatous tissue is friable and bleeds readily, the hazards from the generalized spread of infection and from hemorrhage incident to the trauma of labor are increased.

The fetal prognosis depends, of course, primarily upon the stage of the pregnancy at the time the carcinoma is discovered; the initiation of therapy, either irradiation or surgical, before the period of viability must, of necessity, sacrifice the infant. If the lesion is discovered after the period of viability has been reached, the plan of treatment may include procedures designed to save the baby unless such a method may decrease the chance for destruction of the neoplasm.

Treatment

The treatment of carcinoma during pregnancy is directed toward (1) destroying the malignant lesion and (2) reducing the hazards to the patient from infection and hemorrhage. Because of the small number of cases that have been observed, there is no conclusive weight of evidence pointing to any one method of treatment as being the most effective in accomplishing these aims. There are, however, certain facts which may well be considered whenever this condition is encountered.

Type of Treatment.—It is generally conceded that in most instances cervical cancer is best treated by a combination of radium and deep x-ray therapy. Since this method offers the best prognosis for the nonpregnant patient, there seems to be no reason for advocating, during pregnancy, radical surgical procedures de-

signed to remove the malignancy. The possible exception is the extremely early lesion confined to a small area on the cervix.

The amount of irradiation necessary to destroy the lesion is comparable to that in the absence of pregnancy. The presence of the pregnancy, however, may require an alteration in the routine of administration. The total amount of deep x-ray therapy should be an amount sufficient to deliver 3,000 r. to each parametrial area. This may be given through two anterior and two posterior lower abdominal portals. Occasionally, lateral portals are used. The total radium dosage should approximate 5,000 mg. hours, of which one-third is delivered to the body of the uterus and two-thirds to the cervix and surrounding parametrium. Patient 3 (Table II), when first examined, had been free from symptoms and had a lesion confined to one lip of the cervix. The initial deep x-ray therapy (1932) consisted of a total skin dosage of only 4,200 r. This, plus the 3,100 mg. hours of radium, retarded the growth of the neoplasm until 1937 at which time extension was first noted. Although further therapy was then given, the patient died of carcinoma. While it is impossible to state with any degree of certainty, it seems probable that adequate initial treatment might have eradicated the lesion.

Postirradiation pelvic lymphadenectomy as suggested by Taussig¹¹ for the treatment of early cervical cancer may improve the results over those with x-ray and radium alone. If it is true that lymphatic extension is hastened because of the pregnancy, the glands should be involved at an earlier stage than in the nonpregnant patient, and failure to cure early lesions may be the result of small foci in the lymph nodes which escaped destruction by the x-ray. We intend to make this addition to the treatment in the future.

Hemorrhage.—One of the hazards of delivery from below is bleeding. If the lesion is extensive and involves the greater part of the cervix, dilatation will not occur, but the friable vascular tissue may tear in all directions, resulting in exsanguinating hemorrhage. In the face of such a lesion, abdominal delivery is definitely indicated. Three of the patients delivered by us were delivered vaginally. In all, the lesion was relatively small and no unusual hemorrhage was encountered.

Infection.—While the danger from hemorrhage is lessened by cesarean section, that from infection is increased. A sloughing cervical lesion is always infected, commonly with streptococci. Through the placental site and the uterine wound, invasion of the organisms directly to the blood stream and peritoneal cavity may occur. If the lesion is fungating and infected, cesarean subtotal hysterectomy is the safest procedure. The argument that the cervical stump is a less advantageous place from which to irradiate the pelvis is not upheld by statistics on the treatment of stump cancer, which indicate that the results of treating this condition are better than when the uterine corpus is present.⁷⁻¹⁰

The administration of the sulfonamides by mouth pre- and postoperatively undoubtedly will reduce the danger from infection. As in other operative procedures, however, these drugs cannot be expected to compensate for poor technique and faulty judgment. Every effort to reduce infection in the local lesion prior to operation should be made.

The Fetus

While the life of the fetus is important, it cannot, in most instances, be weighed against that of the mother. During early pregnancy there can be

no question but that definitive therapy directed toward destroying the carcinoma be instituted as soon after the diagnosis is established as is possible. If the lesion is discovered after the period of presumed viability has been reached, little except advancement of the lesion can be gained by withholding treatment. However, should the lesion be far advanced with complete infiltration of the vaginal vault and pelvis so that no possible hope for cure exists, the pregnancy may be allowed to continue until a time at which there seems to be little question but that the infant will survive.

At the borderline, when a delay of one or two weeks may bring the baby to viability, a temporary delay in instituting treatment may be permissible. A more logical procedure in such cases, however, is to apply radium to the cervix and possibly even in the cervical canal as an initial step before the uterus is emptied. This procedure was carried out in Cases 1, 3, and 6, and in all, after a delay of from two to six weeks, a living baby was born.

If external irradiation is given over the uterus during early pregnancy, and abortion does not follow, fetal abnormalities occur in a high percentage of cases.¹² Microcephalic idiocy has been the defect most commonly noted. Murphy advises artificial interruption of any pregnancy which continues after irradiation.

Summary of Treatment

First Trimester.—X-ray therapy should be started as soon as the diagnosis is established. In most instances, abortion occurs during the third week of the treatment. Should this not occur or should it be incomplete, curettage may be carried out with little danger after the size of the lesion and infection in the cervix have been reduced by the irradiation. The external irradiation is carried to a calculated dosage of 3,000 r. to each parametrium and is followed by radium insertion after the uterus is empty. The total radium dosage consists of at least 5,000 mg. hours, of which one-third is delivered to the uterus and two-thirds to the cervix and surrounding parametrium.

Second Trimester.—Early in the second trimester, treatment like that described above may be initiated. The interruption of pregnancy is less consistent, however, and effective irradiation of the pelvis is diminished due to the increased size of the uterus.

During the late second trimester, an initial surface interstitial and/or intracervical application of radium may be followed, after the reaction has subsided, by cesarean hysterectomy. A complete course of x-ray therapy, which may be started as soon as the wound is healed, is followed by the intrauterine application of radium to complete the total dosage. Delivery from below is contraindicated unless the lesion is very small.

Third Trimester.—Treatment during the third trimester is much like that during the latter part of the second. There is no reason for delaying the initial treatment of the cancer. The larger the baby the more dangerous becomes vaginal delivery, and the closer to term the more apt are local manipulations to precipitate labor. In the majority of cases, abdominal delivery is the method of choice. Patient 3 was delivered vaginally two weeks after the radium implantation. She was admitted in active labor with the cervix well dilated. Since the infant was small, delivery from below was allowed. Patient 4 was examined near term for bleeding, and since she was in labor and because the diagnosis of carcinoma had not been established, delivery from below was permitted. The diagnosis of carcinoma was not made in Patient 5.

Summary:

The existence of pregnancy and carcinoma of the cervix together is unusual and presents a difficult problem in therapy, but an unusual opportunity to treat early lesions may present itself. The prompt and thorough investigation of bleeding during pregnancy is an important step in diagnosing the condition and may be responsible for saving the life of the patient. In most instances, radical surgical procedures have no place in treatment since the results from combined irradiation are equally as good. A high fetal mortality is inevitable since it usually is unwise to resort to methods of treatment which attempt to preserve the fetus but which may decrease the chances for cure of the neoplasm.

Of the three patients in this series eligible for consideration, two (67 per cent) survived longer than five years after treatment; only one, however, is free from evidence of carcinoma.

References

1. Danforth, W. C.: AM. J. OBST. & GYNEC. 34: 365, 1937.
2. Hofbauer, J.: AM. J. OBST. & GYNEC. 25: 779, 1933.
3. Peller, S.: Wien. klin. Wchnschr. 38: 892, 1925.
4. Emge, L. A.: AM. J. OBST. & GYNEC. 28: 682, 1934.
5. Richman, S., and Goodfriend, M. J.: Am. J. Roentgenol. 48: 677, 1942.
6. Maino, C. R., and Mussey, R. D.: AM. J. OBST. & GYNEC. 47: 229, 1944.
7. Scheffey, L. C.: J. A. M. A. 107: 837, 1936.
8. Ward, G. G.: AM. J. OBST. & GYNEC. 41: 660, 1941.
9. Behney, C. A.: AM. J. OBST. & GYNEC. 40: 780, 1940.
10. Watkins, R. E.: Northwest. Med. 40: 172, 1941.
11. Taussig, F. J.: Am. J. Roentgenol. 45: 813, 1941.
12. Murphy, D. P.: AM. J. OBST. & GYNEC. 18: 179, 1929.

PRIMARY CARCINOMA OF THE FALLOPIAN TUBE*

ROBERT M. MITCHELL, M.D.,† AND ROY W. MOHLER, M.D., Sc.D.,‡
PHILADELPHIA, PA.

(From the Lying-In Division of the Pennsylvania Hospital)

THE objective of this article is threefold: (1) to submit a case report of primary carcinoma of the Fallopian tube discovered on routine microscopic examination of segments removed at the time of an elective cesarean section, (2) to bring the literature up to date in so far as possible, and (3) to again mention briefly the salient points regarding primary carcinoma of the Fallopian tube, some of which have been set forth in previous articles, even though this case is not entirely comparable with respect to diagnosis, since it was accidentally rather than preoperatively suspected.

According to Sanger and Barth,¹ Raynaud reported the first case of primary carcinoma of the Fallopian tube in 1847, but the first pathologic description was given by Rokitsansky in 1861; Orthmann in 1886 reviewed the thirteen cases in the literature previous to that time only to exclude them as representing metastatic disease from a primary source in the uterus or ovary. Hence, he receives priority in reporting the first undoubted case of primary car-

*Presented at a meeting of the Philadelphia Obstetrical Society, Dec. 7, 1944.

†Assist. Surg. (R), U. S. Public Health Service, Resident House Physician, Lying-In Division of Pennsylvania Hospital.

‡Attending Obstetrician and Gynecologist, Chief of the Out-Patient Department, Lying-In Division of Pennsylvania Hospital.

cinoma of the tube. Many authors have contributed to a slowly growing list of case reports until to date some 449 cases have been recorded. Parsons² made an interesting compilation starting with Orthmann's original case in 1886. Sanger and Barth collected 17 cases in 1895. Peham found 63 cases in 1902. Doran reviewed the 100 cases reported up to 1910. Liang gathered 214 cases in 1926, and this was increased in 1929 to 230 cases by Wharton and Krock who also added 14 authentic specimens, 5 of them from Johns Hopkins Hospital and the surrounding hospitals. Nurnberger reviewed the literature again from 1886 to 1931 and was able to find 301 cases. To this number Robinson added 48 cases bringing the total to 349 up to 1935. Following this review by Parsons in 1939, Martzloff³ reported 34 new cases "from 1935 to 1938 inclusive" bringing the total to 383. Mullins and Mosteller⁴ state that Martzloff reported 392 cases up to 1938 and to this number added 35 additional cases collected from the foreign and domestic literature up to July, 1942, raising the approximate total to 427. In again reviewing the foreign and domestic literature from January, 1939, to December, 1944, we have been able to collect some 66 cases by the following authors: one case each—Cabot Case #25041,⁵ P. Quinto,⁶ J. N. Ficenec,⁷ J. Ostreil,⁸ K. Vacha,⁹ K. H. Martzloff,³ H. A. Baron,¹⁰ H. Wilson,¹¹ A. Zacho and E. Christensen,¹² T. Murasugi et al.,¹³ Cabot Case #27102,¹⁴ W. Selberg,¹⁵ H. L. Gardner and J. C. Cain,¹⁶ E. Hoenig and M. P. Warner,¹⁷ D. F. Mullins and R. Mosteller,⁴ D. Y. Keith,¹⁸ and J. E. Hobbs¹⁹; two cases each—D. N. Henderson,²⁰ W. D. Fullerton,²¹ J. A. Tuta and W. A. Stuhr,²² J. O. Baker and A. Blais²³; three cases—T. S. Kimball et al.²⁴; five cases—J. L. McGoldrick et al.²⁵; six cases—J. Platz,²⁶; seven cases—C. Ambre²⁷; eight cases—L. Parsons²; twelve cases—M. Berger.²⁸

As Martzloff³ and others point out, errors of tabulation creep into the literature and almost all of the reports reveal the same discrepancies. Table I shows Parsons' compilation supplemented by additional reports.

TABLE I. TABULATION OF PARSONS' COMPILATION SUPPLEMENTED BY ADDITIONAL REPORTS

AUTHOR	CASES	YEAR
Orthmann	1	1886
Sanger and Barth	17	1895
Peham	63	1902
Doran	100	1910
Liang	214	1926
Wharton and Krock	244	1929
Nurnberger	301	1886-1931
Robinson	349	1936
Martzloff	383	1940
Mullins and Mosteller	427	1943
Authors'	449	1944

Incidence

The incidence in various hospital centers is roughly similar. Wharton and Krock²⁹ report five cases among 35,000 gynecologic patients at Johns Hopkins Hospital. Gupta³⁰ in Calcutta found one specimen among 6,000 patients with pelvic disease. Barrows³¹ noted three cases among 30,000 patients on the gynecologic wards at the Bellevue Hospital in New York City. Holland³² reported nine cases in 10,000 complete salpingectomies done at the Mayo Clinic. Anspach³³ found one case in 19,439 patients on the gynecologic service at the University Hospital in Philadelphia. Fullerton estimates one primary carcinoma in every 1,000 salpingectomies from his studies made in Cleveland. Hoffman and Anspach³⁴ report the condition once in 4,275 cases admitted to the gynecologic service of the Jefferson Hospital in Philadelphia over a period of nine years. We have been able to verify but this one case in 6,149 surgical specimens of Fallopian tubes taken for microscopic examination at the Pennsylvania Hospital since the founding of the Ayer Clinical Laboratory in 1898. The frequency of primary carcinoma of the tube among tumors of the genital tract is found to vary in the literature from 0.03 per cent to 1.35 per cent and is considered to average about 0.5 per cent. Johnson and Miller³⁵ report a case in a girl 18 years of age and Fullerton²¹ a case in an 80-year-old woman. Age apparently has little or no influence on the disease. However, the greatest incidence occurs in the fifth decade. Unilateral involvement occurs in 70 per cent of the cases and bilateral lesions occur in 30 per cent of the cases. Secondary carcinoma of the Fallopian tube is ten times as frequent as primary carcinoma. These data are shown in Table II.

TABLE II. INCIDENCE OF PRIMARY CARCINOMA OF FALLOPIAN TUBE FOUND IN VARIOUS HOSPITAL CENTERS

Wharton and Krock	5 cases in 35,000 gyn. patients
Gupta	1 specimen in 6,000 patients
Barrows	3 cases in 30,000 gyn. patients
Holland	9 cases in 10,000 salpingectomies
Anspach	1 case in 19,439 gyn. patients
Hoffman and Anspach	1 case in 4,275 gyn. patients
Fullerton	1 case in 1,000 salpingectomies
Authors'	1 case in 6,149 salpingectomies
Frequency among genital tumors—0.5%	
Age: youngest, 18 yr.; oldest, 80 yr.; greatest incidence in fifth decade	
70%, unilateral; 30%, bilateral; distal two-thirds, common site	

Etiology

Although the etiological factor in primary carcinoma of the Fallopian tube is unknown, Sanger and Barth,¹ Ewing,³⁶ and others believe inflammatory pelvic disease predisposes, but Peham,³⁷ Wechsler,³⁸ Liang,³⁹ Vest,⁴⁰ Gupta,³⁰ and others do not agree with this hypothesis. Fullerton²¹ states that the frequency of coincident tuberculosis may be of importance in stimulating formation of benign papillomas which later become malignant.

Pathology

The most frequent site of predilection is the distal two-thirds of the organ. Robinson,⁴¹ in his article quoting Nurnberger, states that the diagnosis of primary carcinoma of the Fallopian tube depends on proving the original source to be endosalpinx. If the anatomic landmarks are still present, this is not difficult. Primary carcinoma involves the mucosa first before extending to the muscularis, while secondary carcinoma usually forms deposits on or in the wall of the tube before it affects the mucosa. According to Robinson,⁴¹ Friedenheim and others described three types of tubal carcinoma: the papillary, the adenomatous, and the alveolar. The earliest variety is the papillary, the latest variety is the alveolar, and the adenomatous apparently is an intervening or intermediary phase. Two or more phases may be demonstrable in the same tube. McGoldrick et al.²⁵ state there are two kinds: the papillary and the infiltrative. The papillary variety grows into the lumen of the tube and the infiltrative variety grows into the wall of the tube. Grossly, the tubes may vary in appearance from the normal salpinx to a greatly distorted, distended, blunt-ending structure. Microscopically, benign tumors generally show but a single layer of epithelial cells covering the folds or lining the pseudoadenomatous spaces formed by adherent folds. These epithelial cells and their nuclei are uniform in size, shape, and staining quality. Malignant growths generally show several layers of epithelial cells which are irregular in size and shape. The irregularity in the staining quality of their large nuclei, which show numerous mitotic figures, is commonplace. Invasion of the tubal wall is usually a late occurrence or may be entirely absent. Tubal epithelium is normal except where involved. It is necessary sometimes to differentiate primary carcinoma of the Fallopian tube from endometrioma, tuberculosis, and chronic inflammation of the tube wall. Willis⁴² states that metastases have been found in the cervix and fundus uteri, ovary, vagina, bladder, kidney, liver, lungs, stomach, large intestines, diaphragm, spleen, skin, and supraclavicular nodes long before the tubal wall has been involved. According to the information based on clinical and pathologic observations made by Cullen,⁴³ Liang,³⁹ Vest,⁴⁰ and others, the lymphatic route is considered to be the only route of dissemination. McGoldrick et al.²⁵ state that the pathways are those along the upper margin of the broad and infundibulopelvic ligaments and ovarian vessels to the iliac, aortic, and lumbar nodes. Metastases have been known to spread via lymphatics of the round ligaments and produce enlarged inguinal lymph nodes. Other methods for development of metastatic lesions by way of continuity, contiguity, transperitoneal migration, and vascular channels must not be overlooked.

Symptoms

Parsons² states: "Bleeding is the earliest and most important single symptom"; and "Pain appears early in the disease in contrast to cancer of fundus or ovary." The symptom complex of intermittent colicky pain associated with a constant, intermittent, or sudden gush of water, yellow or bloody fluid from the vagina, followed by relief of pain, is

suggestive of carcinoma of the Fallopian tube. Robinson¹¹ states that Latzko, in 1915, first noted this symptom complex calling it "hydrops tubae profluens," and, in 1922, Stanca described this symptom complex in detail. Fullerton²¹ says there are no distinctive symptoms. There may be disturbance of menstrual function with some increase in frequency and irregularity. Postmenopausal bleeding may develop. Hydrops tubae profluens, when present, is suggestive, and if the odor of the discharge is foul, necrosis is present.

Diagnosis

Preoperative diagnosis of primary carcinoma of the Fallopian tube is difficult as reflected by the paucity of such cases in the literature. Parsons² considers the most important single fact in the diagnosis "the necessity for suspecting the probable existence of a tubal carcinoma where bleeding has recurred after a negative curettage in an atrophic uterus." Hobbs¹⁹ states that every gynecologist knows that when a woman has a serous or serosanguineous discharge from the cervix, three lesions are to be considered: (1) uterine carcinoma, (2) hydrops tubae profluens, and (3) primary carcinoma of the Fallopian tube.

Treatment

The usual accepted form of treatment is a total hysterectomy and a bilateral salpingo-oophorectomy. Some cases are also given postoperative irradiation with high voltage roentgen therapy. Even so the results are poor. Martzloff,³ in studying cases where postoperative roentgen therapy had been used, concluded that there was an "absence of factual support for such a recommendation." Hobbs¹⁹ suggests leaving the cervix and a portion of the corpus uteri in situ, the cervical and uterine canal acting as a receptacle for later radium insertions. Radium can thus be used in combination with deep roentgen therapy. Clinically, the importance of the fact that 30 per cent of the reported cases are bilateral must not be overlooked. An apparently normal-appearing opposite tube should not prevent a radical procedure.

Prognosis

Parsons² states that "the most important element in consideration of carcinoma of the tube lies not in its rarity but in the fact that it represents the most malignant form not only in genital carcinoma but of carcinoma anywhere in the body." To further emphasize this statement, he mentions his findings of a survival rate less than 4 per cent of three-year cures without roentgen therapy. Fullerton²¹ says that not more than 5 per cent get a five-year cure.

Report of Case

M. B., No. 27,353, a 23-year-old white woman, first registered in the Out-Patient Department of the Lying-In Division of the Pennsylvania Hospital, June 6, 1940. Her prenatal course was entirely uneventful and she was delivered by low forceps and episiotomy, March 4, 1941, of a normal full-term female infant. The postpartum course was normal and the patient was discharged on her tenth postdelivery day. She again registered in the prenatal clinic, May 13, 1942, two months pregnant. This pregnancy was of necessity interrupted on Oct. 1, 1942, by an emergency classical cesarean section for central placenta praevia. The mother's postoperative course was uneventful except for three days' morbidity. She was discharged twelve days postoperative in good condition. This patient was next seen on July 28, 1943, when again she registered in the prenatal clinic two months pregnant. She was classified "abnormal" since she had had a previous caesarean section. The interval history was negative. Her prenatal course proved entirely satisfactory and the patient entered the ward for an elective caesarean section and sterilization. The laboratory examinations were negative. On Feb. 25, 1944, under continuous caudal analgesia, a normal full-term male infant was delivered by a Kerr cesarean section, and Pomeroy's modified Madlener's sterilization operation was performed. The postoperative course was smooth. An excerpt from the description of the operative procedure is as follows: "Both tubes were grasped in their middle thirds and a ligature of No. 3 chromic catgut was tied around each loop. The loops were resected." The specimens of the resected segments of Fallopian tubes were sent to the laboratory for routine confirmation. Gross examination (S. No. 37,636) was as follows: "Specimen in formalin consists of two small pieces

of tissue resembling segments of Fallopian tube. They measure 20 mm. \times 5 mm., and 13 mm. \times 5 mm., respectively. The external surfaces are smooth, glistening, and except for areas of trauma sustained at the time of removal, are not remarkable in appearance. Cross section of the specimens reveals no unusual appearance in the region of the lumina. Sections taken for microscopic study are from the mid- portions of the specimens." Microscopic examination by Dr. John T. Bauer, Director of the Ayer Clinical Laboratory was as follows:

Microscopic Examination.—"The size and contour of the uterine tubes on section are normal. The surface mesothelium is regular, flat and intact. The subserosal tissue and tubo-ovarian ligament are edematous, containing well separated, swollen strands of narrow smooth muscle fibers and a number of dilated but empty arteries, veins and capillaries. A sparse scattering of lymphocytes, occasional monocyte, fibroblast and a rare plasma cell

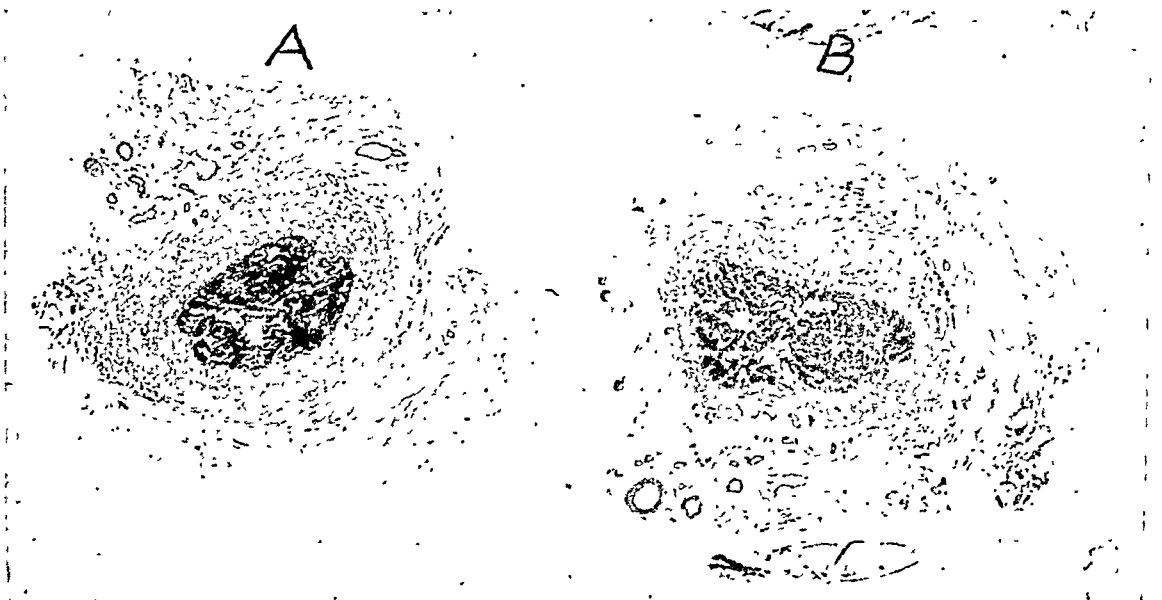


Fig. 1.—Topographical photomicrograph showing sections of normal Fallopian tube (A) and abnormal Fallopian tube (B). (X9.)

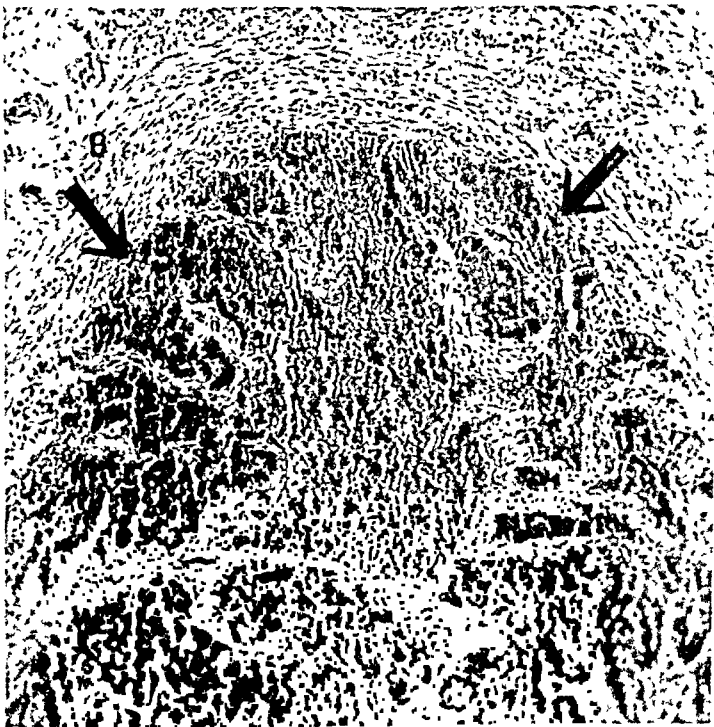


Fig. 2.—Low-power photomicrograph showing region of tumor illustrating sharp line of demarcation between muscularis and endosalpinx. Compare with area shown in Fig. 5. Arrows, A and B, indicate locations shown in Fig. 3 and 4, respectively. (X139.)

exists in the tissue about these vessels. There is a little swelling of the walls of the small veins and arterioles, but the endothelium is not swollen. However, in the deeper subserosa where the underlying muscle fibers become more abundant to form the muscular coat of the uterine tube, lumina of several small vessels become filled but not distended with small pale oval cells containing sparse cytoplasm surrounding pale vesicular nuclei which deviate somewhat at times from an oval shape. The muscle fibers are somewhat pale, swollen, and a little edema exists between them. A few of the small vessels can be traced on serial sections from the subserosa through the muscular coat, pursuing a tortuous course to the submucosa.

"In the lumina of some of these vessels, cells such as those just described seem to be making their passage from the mucosa. The cellular infiltration noted in the subserosa is a trifle more noticeable in the muscular coat and is occasionally accompanied by a polymorphonuclear neutrophile. Thus far all of the changes with the exception of the cells within the lumina of vessels are those customarily observed in a recent intra-uterine pregnancy. From here on, however, the pregnancy changes are overshadowed by those of a low grade malignant, almost benign epithelial neoplasm. The innermost portion of the muscular coat is not clearly demarcated from the submucous and mucosal folds of the tube. Strands of fibrous tissue extend into the lumen, and sheets of the epithelial cells appear to separate some of the muscle bundles and fibers. Capillaries and other small vessels such as those described in the subserosa, penetrate to within a few cells of the solid columns and sheets of proliferative epithelium which replaces most of the normal columnar epithelium that lines the uterine tube. No well defined lumen exists. Instead the columnar epithelium which in places is regular and forms small tubular structures merges with solid masses of epithelial cells that are separated by thin vascularized strands of fibrous tissue which tend neither to form alveoli or papillary stalks. The neoplastic epithelial cells which indistinctly merge with remaining normal columnar epithelium are small with scant, slightly basophilic cytoplasm and surrounding relatively large oval or circular nuclei possessing an increased amount of reticular and granular chromatin which makes them stain a trifle more intensely than the nuclei of normal cells. On the whole these cells are fairly regular. The nuclei vary little in shape and size. Dividing cells are not numerous. There is no reticulum between these solid nests of compact neoplastic cells.

"Throughout the series of sections the solid structures of the neoplastic islands gradually give way to compressed tubular structures and then to the normal arrangement of regular columnar epithelium from which the solid nests have apparently originated. The tumor, despite its local invasiveness and spread through some of the deeper vascular channels to the subserosa, appears relatively benign. Masson's trichrome stain, Masson's silver stain, Mallory's phosphotungstic acid hematoxylin and his modification of Heidenhain's azan-carmine stain confirm the appearance of the hematoxylin-eosin stained preparations."

Pathologic Diagnosis.—"Segments of Fallopian tubes: one segment appears normal, the other segment shows primary carcinoma and both segments show pregnancy changes consisting of swollen smooth muscle fibers."

In view of these findings it was deemed advisable to subject this patient to a total hysterectomy and bilateral salpingo-oophorectomy. This operation was performed three weeks from the day of the Kerr cesarean section. An excerpt from the description of the operation follows: "The uterus was found to be fairly well involuted and healed from the previous operation. Each tube was adherent to the parietal peritoneum at the border of the pelvis and in the right tube there appeared to be some thickening. These adhesions of the tube were at the site of ligation." Doctor Bauer's study of these specimens revealed no further evidence of neoplastic change in the uterus, ovaries, and regions proximal and distal to the points of ligation and resection of the Fallopian tubes. The patient's postoperative course was normal and discharge was granted her thirteen days later, March 30, 1944. The entire hospital stay amounted to thirty-four days. She was again seen in the Special Follow-Up Tumor Clinic May 9, 1944. The note follows: "Weight 110 pounds. The patient feels fine, looks fine, is fine. Pelvis negative. Return in six months." On Nov. 14, 1944, the patient made her second visit to the Tumor Clinic. The physical examination was entirely negative. She had gained 6 pounds in weight and felt fine. Deep roentgen therapy has been instituted.

Discussion

Interesting features of this case are these: (1) the accidental manner in which the tumor was discovered, (2) the occurrence of primary carcinoma of

the Fallopian tube with a normal intrauterine gestation at term, (3) the histopathologic study, and (4) the importance of a routine pathologic examination of tissues.

The small segment of tissue which contained the abnormality was located in the distal two-thirds of the Fallopian tube. This is the area of predilection for carcinoma of the Fallopian tubes. It just happened that this particular region, usually the middle third of the tube, was selected for resection at the time of the Pomeroy modification of Madlener's sterilization operation. Microscopically, this section of tissue proved to contain a primary neoplasm. Which tube was involved remains a mystery.

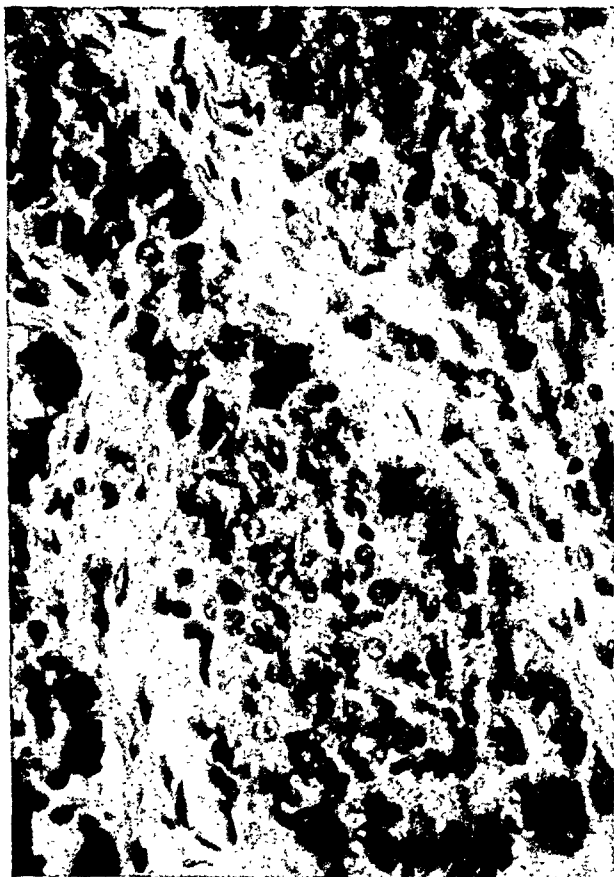


Fig. 3.

Fig. 3.—High-power photomicrograph showing cords of neoplastic cells and a pseudoadenomatous area. Arrow A, Fig. 2. ($\times 580$.)

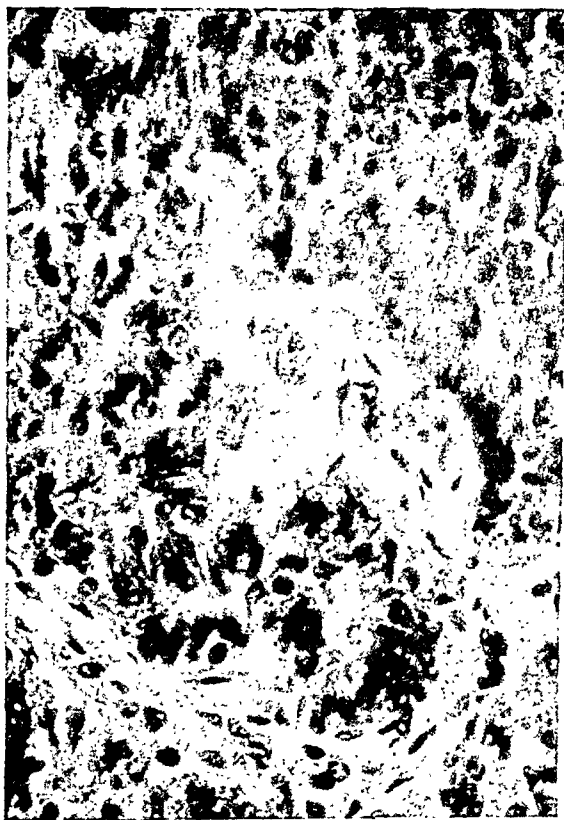


Fig. 4.

Fig. 4.—High-power photomicrograph showing several layers of epithelial cells lining pseudoadenoma, normal columnar tubal epithelium, and cords of neoplastic cells. Arrow B, Fig. 2. ($\times 580$.)

The association of carcinoma of the Fallopian tube with a full-term intrauterine pregnancy is purely coincidental and perhaps of little significance. The only demonstrable pregnancy change in the sections of the Fallopian tube is the swollen smooth muscle fibers. No decidual elements could be detected. Whether or not this region of the tube previously contained a benign papilloma whose growth might have been stimulated by effects of gestation remains conjectural.

The histopathologic study shows that the neoplasm is young enough that the merging of normal columnar epithelium of the endosalpinx with the solid masses of neoplastic cells can be demonstrated (Figs. 3 and 4). The criterion needed for the diagnosis of a primary neoplasm of the Fallopian tube as pointed out by Robinson,⁴¹ quoting Nurnberger, is thus fulfilled. The microscopic description



Fig. 5.—Low-power photomicrograph showing cord formations of neoplastic cells and the tendency for cords to invade tubal wall. Lymph and vascular channel invasion shown. Arrows A and B, indicate locations shown in Figs. 6 and 7, respectively. Pregnancy change consists of swollen smooth muscle fibers. ($\times 130$.)



FIG. 6.



FIG. 7.

Fig. 6.—High-power photomicrograph showing vascular channel invasion by neoplastic cells. Arrow A, Fig. 5. ($\times 580$.)

Fig. 7.—High-power photomicrograph showing lymph channel invasion by neoplastic cells. Arrow B, Fig. 5. ($\times 580$.)

of this specimen fits both Freidenheim's classification and McGoldrick's grouping. This tumor gives the impression of growing toward the lumen of the tube which is the characteristic of the papillary variety. This diagnosis was confirmed by Novak.⁴⁴ Also, in one region of the microscopic section, the continuity of the line of demarcation between muscularis and endosalpinx appears to be broken, suggesting a tendency toward infiltration of the tube wall (Fig. 5). Thus, both varieties of primary carcinoma of the Fallopian tube may be manifest in the same specimen. The adherence of the folds produces the pseudo-adenomatous appearance shown in Figs. 2, 3, 4, and 5. Lymph channels and vascular channels filled with neoplastic cells in the process of migration even at this apparently early stage of carcinomatous growth can be demonstrated (Figs. 6 and 7). The neoplastic cells are described as "small and regular." The cells have a scant basophilic cytoplasm surrounding large oval or circular nuclei which stain more intensely than normal cell nuclei. Few mitotic figures are noted and the nuclei vary little in size and shape. This leads to the idea that this tumor is relatively benign. However, the fact that invasion of the tube wall is suggestive, that neoplastic cells are demonstrable in lymph and vascular channels, that cord formations (carcinoma simplex) of neoplastic cells are prominent, and that there are areas showing several layers of epithelial cells covering the folds or lining the pseudoadenomatous spaces—all direct attention to the fact this lesion may not be as benign or of as low a grade of malignancy as was first suspected. Dr. Bauer's subsequent report on the microscopic appearance of the Fallopian tubes removed at the time of the total hysterectomy and bilateral salpingo-oophorectomy revealed the lesion apparently had been removed in its entirety when the operation for sterilization was done. Perhaps that procedure alone would have accidentally resulted in a cure; but, in the light of the unfavorable prognosis given to this disease, the complete extirpation of the uterus, tubes, and ovaries was considered imperative.

Had the segments of Fallopian tube been examined grossly at the operating table, the lumen identified, and the specimen discarded (rather than sent to the laboratory for routine microscopic confirmation of structure) the new growth probably would not have been discovered until clinically it had reached a much further advanced stage.

References

1. Sanger, M., and Barth, J.: Die Neubildungen der Eileiter: In Martin, A.: Die Krankheiten der Eileiter, Leipzig, 1895, Eduard Besold.
2. Parsons, L.: New England J. Med. 221: 367, 1939.
3. Martzloff, K. H.: AM. J. OBST. & GYNEC. 40: 804, 1940.
4. Mullins, D. F., and Mosteller, R.: AM. J. OBST. & GYNEC. 45: 1042, 1943.
5. Cabot Case No. 25041, New England J. Med. 220: 161, 1939.
6. Quinto, P.: Riv. ital. di gynec. 22: 3, 1939.
7. Ficenes, J. N.: Ginek. polska 18: 65, 1939.
8. Ostril, J.: Ceskoslov. gynaek. 18: 25, 1939.
9. Vacha, K.: Ceskoslov. gynaek. 18: 205, 1939.
10. Baron, H. A.: Canad. M. A. J. 43: 118, 1940.
11. Wilson, H.: Roy. Melbourne Hosp. Clin. Rep. 11: 41, 1940.
12. Zacho, A., and Christensen, E.: Acta obst. et gynec. Scandinav. 21: 63, 1941.
13. Murasugi, T., Kawasima, T., and Nakai, K.: Jap. J. Obst. and Gynec. 24: 43, 1941.
14. Cabot Case No. 27102: New England J. Med. 224: 427-428, March 6, 1941.
15. Selberg, W.: Dermat. Wehnschr. 113: 579, 1941.
16. Gardner, H. L., and Cain, J. C.: AM. J. OBST. & GYNEC. 42: 522, 1941.
17. Hoenig, E., and Warner, M. P.: M. Rec. 155: 271, 1942.
18. Keith, D. Y.: Kentucky M. J. 41: 74, 1943.
19. Hobbs, J. L.: South. M. J. 35: 733, 1942.
20. Henderson, D. N.: AM. J. OBST. & GYNEC. 37: 521, 1939.
21. Fullerton, W. D.: AM. J. Surg. 48: 167, 1940.
22. Tutu, J. A., and Stuhr, W. A.: Am. J. Clin. Path. 11: 864, 1941.
23. Baker, J. O., and Bliss, A.: Canad. M. A. J. 46: 67, 1942.

24. Kimball, T. S., Sanford, H. E. and Brown, A. F.: *California & West. Med.* 57: 351, 1942.
25. McGoldrick, J. L., Strauss, H., and Rao, J.: *Am. J. Surg.* 59: 555, 1943.
26. Platz, J.: *Arch. f. Gynäk.* 170: 604, 1940.
27. Ambre, C.: *Gynécologie* 38: 89, 1939.
28. Berger, M.: *Lijeén. vjes.* 63: 93, 1941.
29. Wharton, L. H., and Krock, F. H.: *Arch. Surg.* 19: 848, 1929.
30. Gupta, N.: *J. Obst. & Gynaec. Brit. Emp.* 38: 839, 1931.
31. Barrows, D. N.: *AM. J. OBST. & GYNEC.* 13: 710, 1927.
32. Holland, W. W.: *Surg. Gynec. & Obst.* 51: 683, 1930.
33. Anspach, B. M.: *AM. J. OBST. & GYNEC.* 20: 571, 1930.
34. Hoffman, J., and Anspach, B. M.: *AM. J. OBST. & GYNEC.* 22: 424, 1931.
35. Johnson, W. O., and Miller, A. J.: *Ann. Surg.* 93: 1208, 1931.
36. Ewing, J.: *Neoplastic Diseases: A Treatise on Tumors*, ed. 3, Philadelphia and London, 1928, W. B. Saunders Co., p. 653.
37. Peham: *Ztschr. f. Heilk.* 24: 317, 1903.
38. Wechsler, H. T.: *Arch. Path.* 2: 161, 1926.
39. Liang, Z.: *Arch. f. Path. Anat.* 259: 577, 1926.
40. Vest, C. W.: *Bull. Johns Hopkins Hosp.* 25: 305, 1914.
41. Robinson, M. R.: *AM. J. OBST. & GYNEC.* 32: 84, 1936.
42. Willis, E. A.: *The Spread of Tumors in the Human Body*, London, 1934, J. and A. Churchill, p. 283.
43. Cullen, T. S.: *Bull. Johns Hopkins Hosp.* 22: 20, 1911.
44. Novak, E.: Personal communication.

AQUINONE* DURING LABOR; ITS EFFECT ON THE PROTHROMBIN LEVEL OF THE NEWBORN INFANT†

HERBERT E. SCHMITZ, M.D., AND GEORGE BABA, M.D., CHICAGO, ILL.

(From the Department of Obstetrics and Gynecology, Loyola University School of Medicine, and the Lewis Memorial Maternity Hospital)

A STUDY of prothrombin levels in the newborn infant requires the consideration of many factors. Recent literature reports the prothrombinopenic effects of drugs, such as certain barbiturates^{4, 5, 17} and salicylates,¹⁵ as well as the beneficial effect on newborn infants, of Vitamin K administration to laboring mothers. Furthermore, the institution of early extra feeding schedule has been shown to have a prophylactic effect against the development of prothrombinemia in the newborn.^{13, 14} Thus, determinations of the prothrombin level in newborn infants lose their significance unless correlated with maternal conditions prior to parturition and with feeding schedules.

Errors in technique should be reduced to the minimum by the adoption of certain standards. The elements of human error can be ignored when the same personnel handles all the procedure. The effect of temperature must be eliminated by allowing enough time for the reagents to reach room temperature. This is important, since the prothrombin clotting time will be materially prolonged by the use of reagents below the prevailing room temperature.⁸ The ideal in controls is reached by the use of two or three newborn infants past the sixth postnatal day and with normal clotting time (100 per cent) for at least the last two days.

Procedure

Freshly extracted Bacto-thromboplastin² was used in the dilution wherein the clotting time of normal blood falls in the range of 25 to 30 seconds. Thirty to forty cubic millimeters

*Aquione supplied by a grant from Ernst Bischoff Co., Inc., Ivoryton, Conn.

†Presented before a regular meeting of the Chicago Gynecological Society, Nov. 17, 1944.

of the free-flowing blood from a lanced heel was immediately mixed on a clean slide with 10 c.mm. of the reagent. The clotting time was determined by tilting the glass back and forth until the clot formed.

$$\text{Clotting time in per cent} = \frac{\text{Clotting time of normal}}{\text{Clotting time of patient}} \times 100.$$

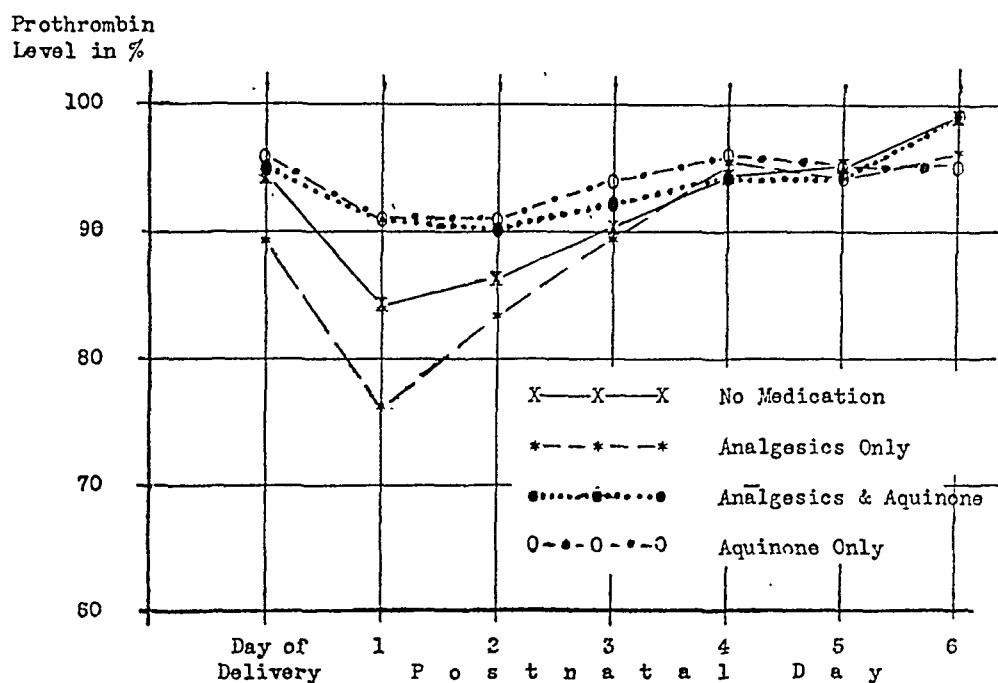


Fig. 1.—Average prothrombin level of the newborn infants.

TABLE I. TOTAL NUMBER OF CASES DETERMINED, TOTAL PERCENTAGE (PROTHROMBIN LEVEL), AND AVERAGE LEVEL

	NO MEDICATION		ANALGESICS ONLY		ANALGESICS AND AQUINONE		AQUINONE ONLY	
Day of delivery								
No. of cases	137		43		63		23	
Total per cent	12902		3821		6011		2216	
Average per cent		94		89		95		96
Postnatal 1								
No. of cases	166		53		74		27	
Total per cent	13930		4055		6775		2457	
Average per cent		84		76		91		91
Postnatal 2								
No. of cases	163		52		75		28	
Total per cent	14148		4310		6796		2548	
Average per cent		86		83		90		91
Postnatal 3								
No. of cases	153		51		74		28	
Total per cent	13828		4541		6857		2642	
Average per cent		90		89		92		94
Postnatal 4								
No. of cases	149		48		67		27	
Total per cent	14116		4500		6354		2601	
Average per cent		94		95		94		96
Postnatal 5								
No. of cases	140		49		66		27	
Total per cent	13320		4621		6238		2583	
Average per cent		95		94		94		95
Postnatal 6								
No. of cases	138		48		63		23	
Total per cent	13711		4650		6265		2185	
Average per cent		99		96		99		95

TABLE II. THE DAY OF MINIMUM PROTHROMBIN LEVEL

	NO MEDICATION		ANALGESICS ONLY		ANALGESICS AND AQUINONE		AQUINONE ONLY	
TOTAL NO. OF CASES	165		56		80		30	
No drop								
No. of cases	16		0		13		7	
Per cent of cases	10		0		16		23	
Day of delivery								
No. of cases	14		7		12		3	
Per cent of cases	8		12.5		15		10	
Postpartum 1								
No. of cases	61		33		17		7	
Per cent of cases	37		59		21		23	
Postpartum 2								
No. of cases	44		13		17		9	
Per cent of cases	27		23		21		30	
Postpartum 3								
No. of cases	22		2		13		1	
Per cent of cases	13		4		16		3	
Postpartum 4								
No. of cases	7		0		6		3	
Per cent of cases	4		0		7.5		10	
Postpartum 5								
No. of cases	1		1		2		0	
Per cent of cases	1		2		2.5		0	

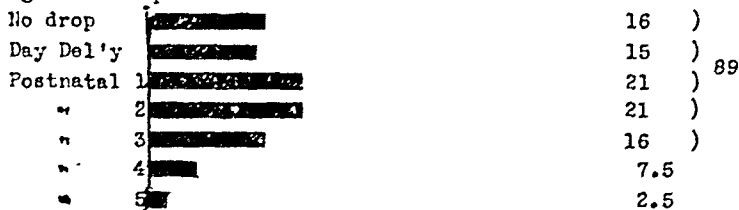
No Medication



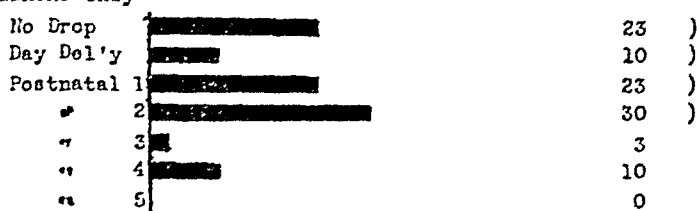
Analgesics Only



Analgesics & Aquinone



Aquinone Only



10 20 30 40 50 60 70 80

Fig. 2.—The day of minimum prothrombin level (in per cent).

This study was conducted by the same two residents. Reagents were not used until they were of room temperature. Separate controls were used in the different nurseries, since the temperatures varied in each. The average of two or three infants past the sixth postnatal day, having 100 per cent clotting time for at least the two preceding days, was used for control.

Analysis of Data

A total of 231 unselected cases of newborn infants was investigated. They were classified according to whether the laboring mother had received no medication, some form of analgesia (usually cyclopal sodium), both analgesia and aquinone, or only aquinone. The amount of analgesics given differed with the duration of labor, but only one ampule of aquinone was given intramuscularly in a twenty-four-hour period. Prothrombin levels were made on the day of delivery and for six days thereafter.

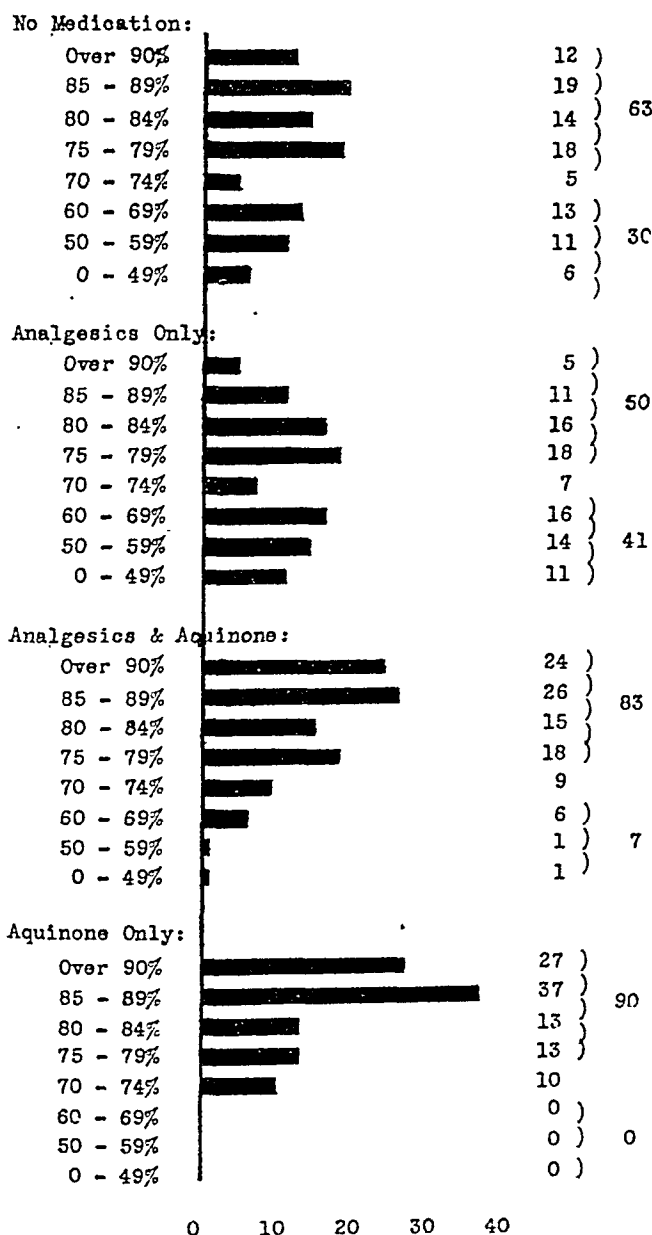


Fig. 3.—Prothrombin level on the first day of minimum level.

The data were analyzed to determine the minimum level and the day by which this level was reached. When the average levels are plotted (Table I), a precipitous drop by the first day is shown for the groups where no aquinone was used (Fig. 1), while the groups with aquinone showed but a slight drop.

Further analysis, however, will correct the misleading implications of generalizations as in Fig. 1 (See Tables II and III, and Figs. 2 and 3). The classification of "no drop" is used to designate those cases in which the minimum level never fell below the 92 per

TABLE III. PROTHROMBIN LEVEL ON THE FIRST DAY OF MINIMUM LEVEL

	NO MEDICATION		ANALGESICS ONLY		ANALGESICS AND AQUINONE		AQUINONE ONLY	
TOTAL NO. OF CASES	165		56		80		30	
Over 90 per cent	20		3		19		8	
No. of cases								
Per cent of cases	12		5		24		27	
85-89 per cent	32		6		21		11	
No. of cases								
Per cent of cases	19		11		26		37	
80-84 per cent	24		9		12		4	
No. of cases								
Per cent of cases	14		16		15		13	
75-79 per cent	30		10		14		4	
No. of cases								
Per cent of cases	18		18		18		13	
70-74 per cent	9		4		7		3	
No. of cases								
Per cent of cases	5		7		9		10	
60-69 per cent	22		10		5		0	
No. of cases								
Per cent of cases	13		16		6		0	
50-59 per cent	12		8		1		0	
No. of cases								
Per cent of cases	11		14		1		0	
0-49 per cent	10		6		1		0	
No. of cases								
Per cent of cases	6		11		1		0	

cent level. This is because 8 per cent represents only 2 seconds difference in the clotting time (see *Procedure*) and is within the margin of error. Others represent the first day of minimum level. When two or more successive days differed by only 2 per cent, the first day on which the low level occurred was regarded as the first day of minimum level:

Day of delivery	Postnatal					
--	i	ii	iii	iv	v	vi
--	--	--	82	80	84	

The postnatal iii day was taken. Again, the 2 per cent represents $\frac{1}{2}$ second difference in the clotting time and is therefore not measurable.

As can be seen from Fig. 2, the day of minimum level is not as clear cut as one is led to believe when only the averages are considered (Fig. 1).

With no medication, 82 per cent were at the minimum level by the second full postnatal day, but 64 per cent dropped to the minimum level on the first and second day. When analgesics were used, 94 per cent dropped to the minimum level by the third day, but 59 per cent were at the minimum level on the first postnatal day. When analgesics and aquinone were both used, 89 per cent fell to the minimum level by the third day but the fall was spread fairly evenly over the four days. When aquinone alone was used, 86 per cent fell to the minimum level by the third postnatal day, with the greatest number (30 per cent) occurring on the second postnatal day.

A study of the actual amount of fall to the minimum level is interesting (Fig. 3). The percentage of cases remaining above the 75 per cent minimum level is as follows: no medication, 63 per cent; analgesics alone, 50 per cent; both analgesics and aquinone, 83 per cent; aquinone alone, 90 per cent. More significant than the above is the percentage of cases falling below the 70 per cent level, since many clinicians consider values below this level to be an indication for vitamin K therapy (in diseases accompanied by prothrombinemia), and values below 40 as definitely in the danger zone. Where no aquinone was used, the percentages were 30 per cent and 41 per cent for the "no medication" group and the "analgesics only" group, respectively, while where the aquinone was used, the percentage was 8 and 0 for the "aquinone-analgesic" group and the "aquinone alone" group, respectively.

Miscellaneous Finding

In this small series no definite conclusion can be drawn, but, nevertheless, certain incidental observations are set forth. Icterus of varying degree was frequently seen in spite of the high or normal prothrombin level (over 92 per cent). In some, the icterus was quite marked in spite of the normal clotting time. On the other hand, other cases with prothrombin level below 40 per cent manifested no icterus.

Discussion

A review of the literature brings out conflicting views regarding the value of vitamin K in obstetrics. Parks and Sweet¹² conclude that it has no evident effect in reducing the incidence of neonatal hemorrhage. Hellman and his associates,⁷ on the other hand, contend that the incidence of hemorrhage in the non-vitamin K group is too striking to be mere coincidence. Maumenee and associates¹¹ report a greater incidence of retinal hemorrhage in the non-vitamin K group than in the vitamin K group.

For a proper evaluation of any antihemorrhagic factor, it is important that all variables be considered. Thus, according to Howell's theory of the clotting of blood, prolonged bleeding may result from deficiencies of fibrinogen, calcium, thromboplastin, platelets, and prothrombin, as well as to an excess of the antithrombin factor (heparin). Even when all the component factors are quantitatively normal, bleeding may still be prolonged as in the case of a hemophiliac. Then, too, must be considered such factors as the degree and the extent of trauma initiating bleeding.

The role of hypoprothrombin in the hemorrhagic disease of the newborn may best be summarized by quoting Eastman: "Hypoprothrombinemia introduces . . . a new concept of hemorrhagic diathesis in the newborn. Far from being a disease entity unto itself, it represents, simply, an extreme degree of a condition hypoprothrombinemia, which all newborn infants exhibit to a certain extent and in various gradations. Unless the plasma prothrombin level is extremely low, the hypoprothrombinemia may be without clinical manifestation. However, if birth trauma, anoxia, and other causes of bleeding are superimposed upon it, the prothrombin lack must necessarily play a part in the duration and, therefore, the extent of bleeding. . . ."

Theoretically, circumstances tending to produce fetal hemorrhage may be present as soon as labor begins. Should intrauterine prothrombinemia exist because of inadequate vitamin K synthesis or intake, and permit the operation of such factors as mechanical pressure, transient relative anoxia, etc., fetal hemorrhage might occur at any time during labor. Hence, it follows that the vitamin K administration should be sufficiently early to eliminate the role of prothrombinemia in the production of hemorrhage.

Conclusions

1. There is a physiologic hypoprothrombin state reaching the minimum level in most cases by the third postnatal day.
2. Labor analgesics in the form of certain barbiturates apparently exert prothrombinopenic effect on the newborn infants.
3. Aquinone to laboring mothers has a prophylactic effect against physiologic or induced prothrombinemia.
4. Icterus of the newborn infant may not be associated with hypoprothrombin state.
5. Aquinone intramuscularly caused no discomforting symptoms.

References

1. Butt, H. R., and Snell, A. M.: Vitamin K, Philadelphia, 1941, W. B. Saunders Co.
2. Difco, Laboratories: Directions for preparing Bacto-Thromboplastin Extract.
3. Eddy, W. H., and Dalldorf, G.: The Avitaminosis, Baltimore, 1941, Williams & Wilkins Co., pp. 427-440.
4. Fitzgerald, J. E., and Webster, A.: J. A. M. A. 119: 1082, 1942.
5. Fitzgerald, J. E., and Webster, A.: AM. J. OBST. & GYNEC. 40: 413, 1940.
6. Hellman, L. M., Moore, W. T., and Shettles, L. B.: Bull. Johns Hopkins Hosp. 66: 379, 1940.
7. Hellman, L. M., Shettles, L. B., and Eastman, N. J.: AM. J. OBST. & GYNEC. 40: 844, 1940.
8. Kato, K., and Poncher, H. G.: J. A. M. A. 114: 749, 1940.
9. Kato, Katsuji: Clinics 2: 33, 1943.
10. Kracke, Roy A.: Diseases of the Blood, ed. 2, Philadelphia, 1941, J. B. Lippincott Co., pp. 633-644.
11. Maumenee, A. E., Hellman, L. M., and Shettles, L. B.: Bull. Johns Hopkins Hosp. 68: 158, 1941.
12. Parks, J., and Sweet, L. K.: AM. J. OBST. & GYNEC. 44: 432, 1942.
13. Pray, L. G.: Journal-Lancet 64: 1, 1944.
14. Salomonsen, L., and Nygaard, K. K.: Acta paediat. 27: 209, 1939.
15. Shapiro, S., Redish, M. H., and Campbell, H. A.: Proc. Soc. Exper. Biol. & Med. 53: 251, 1943.
16. Warner, E. D.: West. J. Surg. 50: 408, 1942.
17. Webster, A., and Fitzgerald, J. E.: S. Clin. North America 23: 85, 1943.

Discussion

DR. AUGUSTA WEBSTER.—The conclusions of both of these essayists are interesting and instructive. Dr. Potter finds, after a careful review of the mortality figures, that "no demonstrable decrease in infant or fetal mortality can be expected to follow the routine administration of vitamin K to all women during labor," and she seems to have proved her point. Dr. Schmidt has added a study on the effect of vitamin K using aquinone. His findings are similar to ours at the County Hospital, including the observation that certain barbiturates lower the prothrombin level of the newborn infant, and that this hypoprothrombin state may be relieved by the administration of vitamin K to the mother during labor.

In these papers, as in all others in the literature to date, there is no demonstration of why some babies with a low prothrombin level bleed, while others do not. It remains for the physiologists to give us the answer. It is certainly true that many babies with a prolongation of prothrombin time do not bleed, but on the other hand, all of the bleeding babies on whom we took the prothrombin level showed a depression below the average physiologic drop of the second and third postnatal days.

To establish a daily normal for babies by the micro method of Kato and Poncher, the blood of 50 babies was checked at the end of each of the first 6 days of life. The averages were 73.8, 59.1, 59.5, 67.3, 75, and 78.9 per cent of normal.

Fifty babies whose mothers had vitamin K orally were also checked daily, and the average prothrombin levels found to be 78.7, 89.3, 87.8, 94, 94.7, and 99.8 per cent. Fifty-four babies whose mothers had synthetic K intravenously or intramuscularly were checked with a daily average of 86.5, 84.7, 91.5, 94.1, 98.7, and 103.6 per cent.

Twenty-eight babies whose mothers had barbiturate analgesics were checked by the same method, and daily averages of 53.1, 38.6, 38, 51.4, 71.1, and 75 per cent were found.

Twelve babies whose mothers were given barbiturate analgesics, and vitamin K during labor were checked, and the averages were 86.4, 87.6, 91.4, 95.4, 98, and 101 per cent.

The neonatal drop in prothrombin is more striking than the figures show. Three babies were excluded from the control series because of clinical bleeding, plus a low prothrombin which made immediate administration of vitamin K seem desirable. One of these had coffee-ground emesis on the second day when the prothrombin was 56 per cent. The other two had continuous bleeding from heel punctures, one on the third day with a prothrombin of 15 per cent, and the other on the fourth day with a prothrombin of 19 per cent. After the administration of vitamin K the prothrombin time rose and the symptoms subsided.

Of the thirty control babies whose mothers had barbiturates, five were withdrawn from the series because of hematoma and continuous oozing at the site of heel puncture. Four of the mothers had received $7\frac{1}{2}$ grains of pentobarbital sodium and one had been given 1 Gm. of sodium Amyl-bromoalyl; all of these improved after the administration of vitamin K.

Seven other babies were called to our attention because of bleeding. These were not in the series originally and, therefore, we do not know what the prothrombin was until

after the onset of symptoms. One baby on the third day had bleeding from the nostrils, and subconjunctival hemorrhages, a coarse tremor, and cyanosis of the face. There was no clot in five minutes. The diagnosis made by the Department of Pediatrics was hemorrhagic disease of the newborn with possible cerebral hemorrhage. One baby had coffee-ground vomitus on the third day with a prothrombin of 36 per cent. One baby showed vaginal bleeding and jaundice on the third day with a prothrombin of 35 per cent. One baby on the fourth day showed a large fluctuant bluish mass on the right cheek, and petechial hemorrhages on the palate with a prothrombin of 10 per cent. A diagnosis of hemorrhagic disease of the newborn was made by the Department of Pediatrics. One baby showed evidence of intracranial damage on the fifth day with a prothrombin of 21 per cent. Another showed palatal bleeding on the fifth day, and a prothrombin of 10 per cent. One showed coffee-ground vomitus on the fifth day, and a prothrombin of 15 per cent. All showed marked increase in prothrombin and cessation of bleeding promptly after administration of vitamin K intramuscularly.

Eight additional babies developed neonatal hemorrhage and were studied:

CASE 1.—The infant had coffee-ground emesis on the second day, with a prothrombin level of 54 per cent. One hour after it received 10 mg. of vitamin K intramuscularly, the prothrombin rose to 66 per cent and in the next two days was 85 and 88 per cent, respectively.

CASE 2.—A large cephalhematoma was noted on the second day. The prothrombin level was 18 per cent and 10 mg. of vitamin K was given. The next day the prothrombin level was 84 per cent.

CASE 3.—Forty-eight hours after birth, this infant's cord began to bleed and was retied. A hematoma formed on the proximal portion and the blood did not clot in five minutes. Ten milligrams of vitamin K were given, and one hour later the prothrombin level was 30 per cent, and the infant was bleeding from the original heel puncture. Another 10-mg. of vitamin K was given, and an hour later the prothrombin level was 48 per cent, the following day it was 67 per cent, and two days later it was 92 per cent.

CASE 4.—On the third day numerous petechiae appeared on the face, neck, and scalp, and subconjunctival hemorrhages were found in the right eye. The prothrombin level was 37 per cent, vitamin K was given, and on the next three days the level was 77, 83, and 92 per cent, respectively.

CASE 5.—This infant vomited bright red blood on the third day, and the prothrombin level was 30 per cent. After vitamin K was given, the level rose to 93 per cent, and was 100 and 103 per cent on the next two days.

CASE 6.—Hematuria appeared on the third day. The prothrombin level was 26 per cent. One hour after vitamin K was given the level rose to 56 per cent. The next day it was 62 per cent, and 80 per cent on the following day.

CASE 7.—Epistaxis occurred on the third day and ecchymoses about the left eye. The prothrombin level was 18 per cent, vitamin K was given, and on the following day the level was 78 per cent.

CASE 8.—On the third day bleeding occurred from excoriations on the chin, and the prothrombin level was 14 per cent. One hour after the administration of vitamin K, the level was 24 per cent, and on the following day 80 per cent.

During the eighteen months of the study which Dr. Fitzgerald and I conducted at the Cook County Hospital, 5,370 normal infants were delivered. Forty-four of these developed signs of hemorrhage in the first few days of life, an incidence of 0.82 per cent. Of these, 42 babies were born of mothers who had received no vitamin K, an incidence of 1.18 per cent for this group. Two were born of mothers who had received some form of vitamin K during labor, an incidence of 0.11 per cent.

We do not believe that it was an accident that 42 out of 44 neonatal hemorrhages occurred in patients who had no vitamin K.

It seems reasonable that fetal mortality as Dr. Potter has shown, would not be altered by the use of vitamin K, since the vast majority of causes of fetal mortality could not be affected by its use. It does seem, however, that infant morbidity may very well be affected. Babies admittedly show a decrease in prothrombin content from the second to fifth day of life, and it is significant that hemorrhage of the newborn infant, when it occurs, appears during this period of lowered prothrombin content.

It is true that prolongation of prothrombin time has not been shown to be a direct cause of hemorrhage, and that many babies with low prothrombin level do not bleed;

however, in our observations every bleeding baby in which the prothrombin level was checked showed a marked depression. The low level appears to be a factor. It seems probable also that there may be unobserved, but not necessarily unimportant, internal hemorrhages in infants (possibly cerebral) which might be lessened if vitamin K were routinely given to women at the onset of labor. Since a striking drop in prothrombin level occurs when the barbiturates are given, it seems that vitamin K is desirable when these analgesics are used.

As Dr. Schmitz has emphasized, in order that the infant may have the advantage of the vitamin K during the trauma of labor, it is preferable that the vitamin be given to the mother before or at the onset of labor, rather than to the infant after birth.

BLOOD PRESSURE IN NORMAL PREGNANCY

GEORGE J. ANDROS, M.D., ANN ARBOR, MICH.

(From the Department of Obstetrics and Gynecology, University of Michigan Hospital)

THE importance of following blood pressure in antepartum patients has been emphasized by obstetricians since the perfection of a simplified sphygmomanometer by Riva Rocci in 1896. Development of hypertension during the period of gestation is recognized as distinctly abnormal.

Precisely what constitutes normalcy in range and trend of blood pressure during uncomplicated pregnancy has been investigated by a number of workers and reported in the American, English, and foreign literature.¹⁻²⁷

Many of these reports are based upon isolated observations or computed averages of variable numbers of readings collected more or less at random during pregnancy. A few investigators have sought to follow blood pressure through the three trimesters by means of serial readings.

In 1925 Simons and Rasmussen³ of the Mayo Clinic reported the blood pressure changes in 27 patients from the second month to term—with several more, seen less often. They noted a slightly irregular but gradual rise in systolic, diastolic, and pulse pressures during pregnancy. Their charts show figures of 107/65.3 at the second month, 116/65.2 at the sixth month, and up to 119/73.7 at term. During the six weeks following delivery there was a gradual fall to 109/66.6.

Somewhat similar results were published by Imaz²⁵ of Buenos Aires in 1939. In his 120 cases the average systolic pressure climbed irregularly from 90 to 116 at term. The diastolic pressure varied between 65 and 70 in the first two trimesters and remained close to 80 throughout the third trimester.

Hare and Karn²⁶ of the London Royal Free Hospital reported in 1929 an investigation of blood pressure, pulse rate, and response to exercise during normal pregnancy. They found the average systolic blood pressure during pregnancy to be lower than the average of nonpregnant women, with a tendency to a lower pressure in the middle period than in earlier weeks, and a slight rise in the last three months. Diastolic pressure during pregnancy was not found to be significantly different from that of nonpregnant women. It was somewhat lower during the first six months and exhibited a steady rise during the seventh month to a maximum in the last month that was higher than the mean for women not pregnant.

Intrapregnancy mean figures were derived from 456 readings made on 106 patients and on readings from 145 other individuals seen once or twice only. Means for nonpregnant women were calculated from readings on young "welfare women," laundry workers, and female medical students.

Cornell¹⁴ in 1929 reviewed 1,000 consecutive cases of pregnancy followed through the three trimesters, calling those cases "normal" whose average systolic pressure remained below 129— as contrasted to other "potentially toxic" and "toxic" groups. In the "normal" group there was a slight, gradual systolic and diastolic drop from the second to the fifth months, and then a rise to a term pressure that was not significantly higher than that found in the first trimester. There was no more than 5 mm. Hg difference between the highest and lowest systolic and diastolic readings at any time during pregnancy.

An impressive study was made by Henry¹⁵ of McGill, published in 1936. The author observed 618 cases through pregnancy and concluded that there is a "marked" fall from the nonpregnancy average in diastolic pressure and a rise in pulse pressure, with some evidence for believing that systolic pressure is lower in the pregnant state.

This conclusion was based upon a comparison of Henry's general average figure of 120/67 for all readings made during pregnancy with a "normal" figure of 120/78, the latter pressure being derived from tables of normal values for women between 20 and 40 years of age prepared by the Sun Life Assurance Company of Canada.

In following this author's average figures according to month and week (during the last month) of pregnancy, little variation from the general average is seen. A low systolic pressure of 115 is noted during the third month and a high of 124 at term. Diastolic pressure is lowest in the fourth month with a reading of 65 and highest in the first week of the ninth month with 72.

Another study is that of Cohen and Thomson¹⁸ of the Boston Lying-In Hospital and published in 1939. In 51 cases these workers found "a definite tendency for average systolic and average diastolic pressure to decrease from the fourth to the ninth lunar month, and to increase during the tenth." The figures accompanying this report reveal a diastolic drop of impressive magnitude, but the decrease in systolic pressure is slight.

Material Used in This Study

This study seeks to determine the range and trend of blood pressure through the course of normal pregnancy. It is unique in that all cases studied presented one or more pressure readings taken prior to the onset of the pregnancy.

The cases included in this series number 300. Two hundred and ninety-three of the patients (97.7 per cent) were white. Six Negro women and one Chinese complete the list. The average age for the group as a whole was 27.7 years. There were 160 primiparous patients (53.3 per cent) and 140 multiparas (46.7 per cent). It should be mentioned that a large majority of the records studied were those of private patients, University Hospital nurses, and other Hospital employees, and former University of Michigan students—in general from the "middle income" bracket.

Each case record included in this study met three requirements:

1. The record presented at least one prepregnancy blood pressure reading taken with the subject in good health.

(There were 661 prepregnancy readings in the study, an average of 2.2 per patient. The length of time between the prepregnancy reading and the onset of the last menstrual period preceding the pregnancy ranged from two days to five years, the time interval being less than one year in 125 out of the 300 cases and less than three years in 225 cases.)

2. The antepartum record of each patient included at least one blood pressure reading taken during each of the three trimesters of the pregnancy.

(There was a total of 3,391 intrapregnancy readings, an average of 11.1 for each patient. In the University of Michigan Maternity Clinic and private obstetrical service, every patient is requested to present herself for a checkup examination once a month for the first six calendar months of the pregnancy, twice a month in the seventh month, and once a week in the eighth and ninth months.)

3. The patient was entirely free at all times during gestation from evidence of toxemia of pregnancy—through sign, symptom, and routine laboratory examination. A systolic pressure of 140 or a diastolic pressure of 90 at any time during the pregnancy eliminated the patient from this study, even in the absence of any other sign or symptom of toxemia.

While blood pressure tends to vary in the same individual under the influence of such factors as recent activity, emotional stress, etc., we feel that a degree of correctness and comparability between prepregnancy and intrapregnancy figures can be expected, since

all readings in this study were taken under similar conditions and with mercury sphygmomanometer.

Intrapregnancy reading were made in the course of routine antenatal checkup examinations. The prepregnancy readings were taken while the patient was in good health during a routine periodic or pre-employment physical examination—made in the University Hospital or University Student Health Service exclusively.

Methods of Analysis

The data obtained from the first 300 case records meeting the above requirements (chosen after an examination of approximately 2,000 records bearing the diagnosis of "Normal Pregnancy") were analyzed by three methods—as follows:

1. The average systolic, diastolic, and pulse pressures for the whole group were computed for each calendar month (and week in the late stages) of pregnancy. These figures were compared with the average prepregnancy pressures for the entire group.

2. The average systolic, diastolic, and pulse pressures for the whole group were computed for each trimester as a unit, and then compared with the average prepregnancy pressures.

3. Each patient's average systolic and diastolic pressures according to trimesters as units were computed. With prepregnancy pressures in each case considered as "zero," deviations for each trimester in every case were calculated and from these the average deviations for the whole group.

Summary of Analyses

The 661 prepregnancy readings in the 300 cases yielded an average "normal" blood pressure of 114.6/72.6 (pulse pressure 42).

This pressure is lower in both systolic and diastolic components than the "normal" 120/78 used by Henry in his study. Robinson and Brucer,³⁸ studying the blood pressure of 3,015 women having readings under 140/90, concluded that the mean figures for women between 25 and 29 years of age were 109.4/66.7 (pulse pressure 42.7).

In comparing the average prepregnancy pressure (systolic, diastolic, and pulse) for the group as a whole with the average intrapregnancy figures for the entire group calculated according to calendar month—or week—of pregnancy (Table I and Fig. 1), no significant deviation in systolic pressure was noted at any time during gestation.

The greatest variation from the prepregnancy "normal" was a rise of 2.15 mm. Hg in the last week before term. The lowest average systolic pressure was 113.08 (second week of eighth month), and the highest was 116.74 (last week before delivery).

Diastolic pressures were consistently lower than the "normal" in the first six and one-half months of pregnancy, but the drop was not at all marked. Deviations ranged from 2.64 to 4.15 mm. Hg below the prepregnancy figure. There was no significant variation from

TABLE I. AVERAGE PRESSURES CALCULATED ACCORDING TO CALENDAR MONTH OF PREGNANCY

	SYSTOLIC	DIASTOLIC	PULSE
Prepregnancy	114.59	72.58	42.01
CALENDAR MONTH OF PREGNANCY			
1	114.00	69.56	44.44
2	114.53	69.85	44.68
3	114.63	68.43	46.20
4	114.43	69.91	44.49
5	114.50	68.98	45.52
6	113.30	69.18	44.12
7 (early)	114.71	68.55	46.16
7 (late)	116.16	70.65	45.51
8 ₁	114.96	71.08	43.88
8 ₂	113.08	69.98	43.10
8 ₃	114.75	71.96	42.79
8 ₄	115.15	72.31	42.84
9 ₁	114.32	72.25	42.07
9 ₂	115.52	73.24	42.28
9 ₃	113.88	72.98	40.90
9 ₄	116.74	75.66	41.08

the prepregnancy diastolic pressure in the last two and one-half months of gestation. Average diastolic readings ranged irregularly from 68.43 at the third month to 75.66 at the last week before delivery.

Average pulse pressure increased with the diastolic fall noted above, varying between 46.20 at the third month down to 40.90 at the third week of the ninth month.

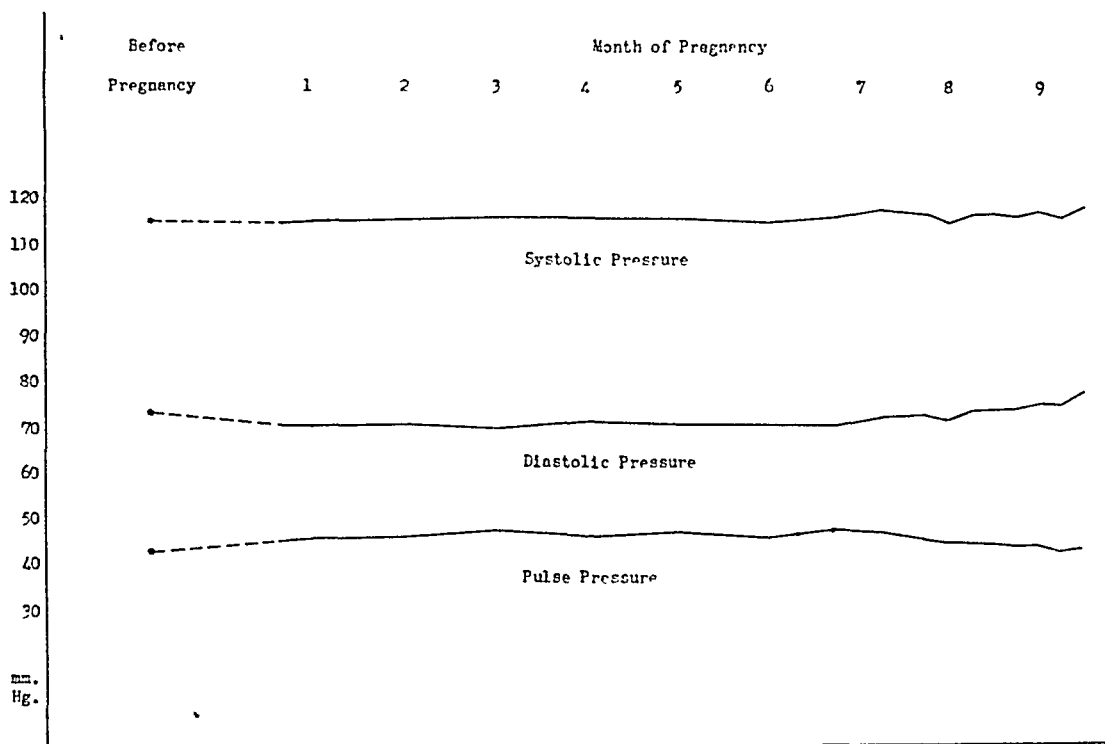


Fig. 1.

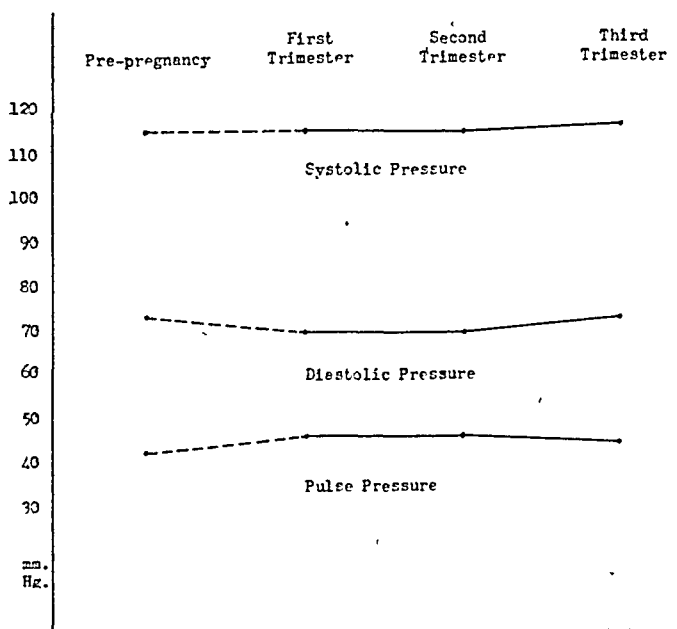


Fig. 2.

TABLE II. AVERAGE PRESSURES CALCULATED ACCORDING TO TRIMESTERS

	SYSTOLIC	DIASTOLIC	PULSE
Prepregnancy	114.59	72.58	42.01
First trimester	114.61	69.02	45.59
Second trimester	113.97	68.99	44.98
Third trimester	115.17	71.97	43.20

When average intrapregnancy pressures for the group as a whole computed according to trimester were compared with the average prepregnancy figures (Table II and Fig. 2), the absence of variation in systolic pressure was striking. No more than 0.62 mm. Hg deviation from the prepregnancy average was found in any of the trimesters. As compared with the prepregnancy figure of 114.59, average systolic pressures of the three successive trimesters were 114.61, 113.97, and 115.17.

The slight fall in diastolic pressure during the first two trimesters again was evident in this method of analysis. The first trimester average diastolic figure (69.02) was 3.56 mm. Hg lower than the prepregnancy figure, and that of the second trimester (68.99) lower by 3.59 mm. Hg. In the third trimester, average diastolic pressure (71.97) was only 0.65 mm. Hg deviated from the average pressure before pregnancy.

Average pulse pressure again reflected the diastolic fall by rising in the first two trimesters.

Calculating the deviation of each patient's systolic and diastolic pressures (according to trimesters as units) from the average prepregnancy figures of each case (considered as zero), and then computing the average deviation for the group as a whole gives results similar to those seen in the other methods of analysis (Table III).

Again there was no significant difference in systolic pressure in each of the trimesters as compared with the pressures taken before pregnancy. In diastolic pressure the small but consistent drop occurring only in the first and second trimesters amounted in this case to average deviations downward of 3.48, and 3.67 mm. Hg, respectively.

TABLE III. AVERAGE DEVIATIONS

(Computed From the Deviations of Each Patient's Pressure by Trimesters From Each One's Prepregnancy Pressures)

	SYSTOLIC	DIASTOLIC
First trimester	+0.09	-3.48
Second trimester	-0.41	-3.67
Third trimester	+0.23	+0.47

TABLE IV. PROPORTIONS OF CASES SHOWING SOME DEGREE OF DEVIATION (BY TRIMESTER UNITS) FROM EACH ONE'S AVERAGE PREPREGNANCY BLOOD PRESSURE

		SYSTOLIC			DIASTOLIC		
		FALL	NO CHANGE	RISE	FALL	NO CHANGE	RISE
First	No.	162	14	124	204	6	90
Trimester	%	54.0	4.67	41.33	68.0	2.0	30.0
Second	No.	152	10	138	204	20	76
Trimester	%	50.7	3.3	46.0	68.0	6.7	25.3
Third	No.	152	6	142	142	10	148
Trimester	%	50.7	2.0	47.3	47.3	3.3	49.4

It is of interest to note that approximately two-thirds of the patients (204 cases or 68 per cent) in this series exhibited some diastolic fall in the first trimester as a unit, and an identical number in the second trimester, but only an approximate one-half of the patients (148 cases or 49.3 per cent) showed a diastolic pressure fall in both the first and second trimesters. The numbers of cases showing falls or rises in systolic pressure tended to be more equal to each other in each trimester. This was also true for the diastolic pressure deviations in the third trimester. (Table IV.)

Discussion

It has been found in this study of 300 cases of normal pregnancy followed through three trimesters that systolic blood pressure does not vary significantly during any period of gestation, nor does it deviate from what might be considered normal systolic blood pressure for healthy nonpregnant women.

By the three methods of analysis used, diastolic pressure consistently has been found to be slightly lower during the first and second trimesters of pregnancy than during the third trimester or in the nonpregnant state. In the third trimester, diastolic figures are not significantly different from those found before the onset of pregnancy.

Whether or not these small but consistent deviations downward in diastolic pressure noted in the first two-thirds of pregnancy are significant is difficult to state. These may well be within the limits of error arising from the use of an instrument such as the sphygmomanometer and from the normal variations in blood pressure. On the other hand, the striking lack of variation in systolic pressure would lead us to consider any consistent variation in diastolic pressure, though small, as being statistically accurate. Theorizing on the etiology of this fall in diastolic pressure during the first two trimesters is beyond the scope of this paper.

The observations presented here should serve indirectly to re-emphasize the fact that any persistent rise in blood pressure during pregnancy should be looked upon with suspicion.

Conclusions

1. Our study reveals that systolic blood pressure does not vary at any time during normal pregnancy from the level for a normal and healthy young woman who is not pregnant.

2. There is evidence that diastolic blood pressure tends to be slightly lower in the first and second trimesters of normal pregnancy than in the normal nongravid state.

3. On the basis of this study it would appear that any persistent, even though slight, increase in either systolic or diastolic pressure during pregnancy should be looked upon as potentially significant.

References

1. Skeel: *Am. J. Obst. & Dis. Women & Children* 59: 369, 1909.
2. Newell: *J. A. M. A.* 64: 393, 1915.
3. Simons and Rasmussen: *Minnesota Med.* 8: 303, 1925.
4. Schulze: *Minnesota Med.* 3: 585, 1920.
5. Wiesner: *Zentralbl. f. Gynäk.* 23: 1335, 1899.
6. Slemons and Goldborough: *Bull. Johns Hopkins Hosp.* 208: 194, 1908.
7. Von Jaschke: *Arch. f. Gynäk.* 94: 809, 1911.
8. Fellner: Quoted by Von Jaschke.
9. Schroeder: Quoted by Von Jaschke.
10. Strassmann, E.: *Arch. f. Gynäk.* 136: 345, 1929.
11. Ride, L.: *Chinese M. J.* 52: 329, 1937.
12. Hinselmann: *J. A. M. A.* 81: 515, 1923.
13. Danforth: *Am. J. Obst. & Dis. Women & Children* 77: 927, 1918.
14. Cornell, E. L.: *AM. J. OBST. & GYNEC.* 18: 42, 1929.
15. Henry, J. S.: *J. Obst. & Gynaec. Brit. Emp.* 43: 908, 1936.
16. Hurst: *Trans. Am. Gynecol. Soc.* 54: 153, 1929.
17. Osborn, G. R.: *South. M. J.* 20: 710, 1927.
18. Cohen, M. E., and Thomson, K. J.: *J. A. M. A.* 12: 1556, 1939.
19. Vaguex, and Nobecourt: *Bull. de Soc. d'Obstet. de Paris*, 1897 (quoted by de Snoo²⁰).
20. de Snoo, K.: *Monatschr. f. Geburtsh. u. Gynäk.* 57: 235, 1922.
21. Engelmann, F.: *Monatschr. f. Geburtsh. u. Gynäk.* 61: 208, 1923.
22. Schwarz, G.: *Arch. f. Gynäk.* 135: 133, 1929.

23. Donaldson: J. Obst. & Gynaec. Brit. Emp. 24: 133, 1913.
24. Litzenberg: Internat. Clinics 4: 141, 1917.
25. Simon, T.: Acta obst. et gynec. Scandinav. 11: 365, 1931.
26. Irving: J. A. M. A. 66: 935, 1916.
27. Faught: Am. J. Obst. & Dis. Women 71: 507, 1915.
28. Hirst: Am. J. Obst. & Dis. Women 71: 507, 1915.
29. Walser, H. C.: J. Michigan M. Soc. 29: 899, 1930.
30. Upshur, J. N.: Virginia M. Monthly 49: 3, 1922.
31. Review of Literature: J. A. M. A. 67: 435, 1916.
32. Kronig, and Futh: Ztschr. f. Geburtsh. u. Gynäk. 51: 249, 1904.
33. Faught, F.: AM. J. OBST. & GYNEC. 11: 633, 1926.
34. Culbertson: Trans. Am. Gynecol. Soc. 54: 153, 1929.
35. Imaz: Semana méd. 2: 100, 1939.
36. Hare, D. C., and Karn, M. N.: Quart. J. Med. 22: 381, 1929.
37. Wollman, H.: Geburtsh. u. Frauenh. 2: 42, 1940.
38. Robinson, S. C., and Bruce, M.: Arch. Int. Med. 64: 409, 1939.

CAUDAL ANALGESIA IN OBSTETRICS WITH SPECIAL REFERENCE TO REPEATED SINGLE BLOCKS

BERNARD J. HANLEY, M.D., AND CHARLES M. MALONE, M.D.,*
LOS ANGELES, CALIF.

(From The Department of Obstetrics and Gynecology of the University of Southern
California School of Medicine)

IN THE last two years, the use of caudal analgesia in obstetrics has increased markedly. From all parts of the country various investigators have published reports of their experience with this analgesia. The great majority of these reports has been based on the continuous caudal technique as advocated by Hingson and Edwards.¹ Our purpose in presenting this paper is to report the use of caudal block in 1,925 obstetric cases at the Los Angeles County Hospital, from July 1, 1942, to July 1, 1944. Since February, 1944, we have used repeated single caudal block for complete analgesia during labor and delivery in a small series of 152 cases. We will present our observations and results in this small series in detail. The disposition of the 1,925 cases is as follows:

1,343	primiparas (Single block)
316	multiparas (Single block)
68	Continuous caudal
42	primiparas
26	multiparas
46	Cesarean section (Single block)
30	primiparas
16	multiparas
152	Repeated single caudal block for analgesia and delivery
161	primiparas
51	multiparas

Technique and Materials

The patient is placed in the modified Sims' position. If we find it too difficult to give the caudal in this position, we change to the knee-chest position. Our skin preparation consists of a scrub with tincture of green soap, followed by ether, then a final covering with Zephiran solution. A sterile drape is placed over the area and the needle inserted.

A 20 gauge, blunt, stainless steel spinal needle is used routinely. We use a wheel of

*All residents on the obstetric service participated in this work, but special credit is due to Lt. (j.g.) Jack Murietta, M.C., U.S.N.R., now in active service, and Hildegarde Wilkinson, M.D.

the anesthetic agent to alleviate the pain while inserting the needle. Following insertion of the needle, aspiration for spinal fluid or blood is then carefully and repeatedly carried out.

For single injection caudal block for delivery, when the presenting part is "crowning," we prefer 2 per cent procaine. The patient is placed on the delivery table, prepared, the history is checked for barbiturate premedication, and the needle is inserted. A dose of 25 to 30 c.c. of the 2 per cent procaine is given, never more. We feel that a dose larger than this is not necessary. Furthermore, it would be dangerous to both mother and child. It is a rare individual that does not obtain complete relief from this medication. The patient is immediately rolled flat on her back to prevent a one-sided block. The delivery is performed without pain and most often without the patient's knowledge. This routine comprised the great majority of cases in our series.

Repeated Single Caudal Block for Analgesia and Delivery

From February, 1944, to July, 1944, we have given repeated single caudal blocks to patients throughout labor for complete analgesia and delivery. This has been tried before at this institution but without success as the drugs used did not give a sufficient period of analgesia to make repeated single blocks applicable. Shortly after the first of the year we obtained tetracaine (pontocaine) $\frac{1}{4}$ per cent in physiologic saline. This dilution contains 2.08 mg. of tetracaine to 1 c.c. of solution.

Varying amounts of the tetracaine, with and without adrenalin, were given at different stages of labor. Our first aim was to achieve a safe analgesic agent for both mother and child and then to find the correct proportions that would make the mother as comfortable as possible. We feel that the safety of the mother and child surmounts all other considerations. We also desire to alleviate the pain of childbirth as completely as possible while at the same time not interfering too markedly with the progress of labor.

At the present time, we give the patient $1\frac{1}{2}$ grains of nembutal with 10 grains of aspirin when her contractions become painful. Demerol, 50 mg., in place of aspirin, has been used recently with very promising results. We attempt to evaluate the patient very carefully as to the probable length of time before delivery can be anticipated and also as to the character of her contractions. When she is having regular uterine contractions of moderate intensity of more than thirty seconds' duration and not more than four to five minutes apart, we give her the first caudal block. We prefer that the head be engaged, that the cervix be 40 to 50 per cent effaced and of at least 3 to 5 cm. dilatation. We request the patient to tolerate the pain as long as she can before the first block is given, assuring her that we can make her completely comfortable for the duration of her labor and delivery. The amount of solution injected with the first caudal block varies somewhat with the individual patient and with the experience of the operator. If the patient is a primipara with hard uterine contractions every two minutes, who is 5 to 6 cm. dilated, we give her 25 c.c. of the $\frac{1}{4}$ per cent tetracaine, with 3 minims of $\frac{1}{1,000}$ adrenalin, in the original injection. If the patient is a multipara, having painful uterine contractions every five minutes, of mild to moderate intensity, and is progressing slowly, we give her 22 to 23 c.c. of the same solution.

We have routinely checked blood pressures in this series of 152 cases. The pressure is taken immediately before the caudal block, immediately after, five minutes after, fifteen and thirty minutes after, and every hour throughout labor; with few exceptions it remained within the range of normal. The patient usually becomes comfortable in five to ten minutes and labor continues; the uterine contractions and fetal heart tones are checked regularly.

The large majority of multiparas are carried through labor and delivery with a single injection. In those cases where a repeat caudal is necessary, because the patient again feels pain, she is prepared, and given a second injection, the usual amount being 20 c.c. If a third injection is given, the amount is also 20 c.c. When the presenting part is on the perineum, the patient is placed on the delivery table and given a last caudal block of 25 to 30 c.c. of 2 per cent procaine. We have found that subsequent injections of tetracaine give less complete and shorter periods of analgesia. Hence, for delivery, we switch to 2 per cent procaine as the anesthetic agent.

The relief from pain with repeated single caudal blocks as employed here is not as complete as that obtained with continuous caudal, as advocated by Hingson and Edwards. We feel it is good psychosomatic medicine to have the patient come out of the analgesia and experience a few painful contractions. She is much more appreciative if you relieve her of pain on two or three occasions than if she is allowed to experience no pain whatever.

Results

Outlet or low forceps are used routinely in this teaching institution for all primiparas. We have found, however, that a good percentage of the primiparas and a large majority of the multiparas will deliver spontaneously with fundal pressure. However, as reported by numerous other investigators, the patient has no urge to bear down and use her voluntary expulsive powers. We feel that the normal progress of labor is very definitely interfered with at this point, but not prohibitively so.

We have found that the shortest labor under single caudal block was twenty minutes. The longest labor under repeated single blocks was fourteen hours and thirty-five minutes. The average duration of labor in multiparas after the first block was two hours and one minute. In primiparas, the average length of labor, after the first caudal block, was five hours and seventeen minutes. We are convinced that the first stage of labor is definitely shortened under caudal analgesia. The second stage is prolonged, however, due to the absence of the voluntary expulsive powers of the mother. The length of the third stage appears unchanged, while the blood loss seems less. Occiput posterior positions are more common, due to the relaxation of the "pelvic sling" and loss of the voluntary expulsive powers. Occiput posterior positions were found in 11.9 per cent of our cases. However, rotation of the head was greatly facilitated by caudal block.

The average length of analgesia produced by a single caudal block, with $\frac{1}{4}$ per cent tetracaine with adrenalin, was two hours and thirty-one minutes in primiparas and one hour and fifty minutes in multiparas. In each case, several patients delivered before the period of analgesia wore off, thus shortening the average length of analgesia. This was particularly true among the multiparas. The period of analgesia was considerably shortened when adrenalin was not added. The length of labor was approximately the same with or without adrenalin. The average number of single caudal blocks given to each patient in our series was: for primiparas, 2.7; for multiparas 1.3.

In this series of 152 cases there were no fetal or maternal deaths attributable to caudal block. There were no infections of the skin, subcutaneous tissue, or deeper structures. There were no serious accidents. A blood pressure drop below 90 mm. systolic occurred in three of the patients. This was entirely asymptomatic and was treated simply by elevating the legs in two instances and by giving a small dose of $\frac{3}{4}$ grain ephedrine sulfate to the other. About 8 per cent of our patients complained of some pain over the sacral region, but this disappeared in a few days. In one case, a very inconsequential pain persisted for ten weeks. There were no known complications or undesirable side results reported by the patients at their postpartum examination, six weeks after delivery.

Eleven major surgical procedures were carried out under single caudal block, using $\frac{1}{4}$ per cent tetracaine. All patients were definitely poor anesthetic risks. There were four extraperitoneal cesarean sections carried out with very good anesthesia. Two vaginal hysterotomies on eclamptic patients in very poor condition were done successfully. Four low cervical cesarean sections were performed, one of which was in a patient with a very severe pre-eclamptic toxemia of pregnancy. There was no maternal or fetal mortality attributable to the anesthesia.

In this entire series of 1,925 patients, from July, 1942, to July, 1944, there have been no maternal deaths from any cause; and no fetal deaths

attributable to this anesthesia. There have been no infections of any kind. One serious accident occurred, which we will describe in detail:

This patient was given a single caudal block for delivery, 25 c.c. of 2 per cent procaine being used. All precautions had been taken to aspirate carefully for blood or spinal fluid. Neither was obtained. Within five to seven minutes, the patient had ceased to breathe and became a dusky hue. Normal blood pressure was maintained for fifteen minutes then dropped to shock level. Artificial respiration was carried out and stimulants were given for one hour. At about that time she began to breathe spontaneously. Fetal heart tones became somewhat rapid, but the patient was delivered of a crying baby following recovery. Anesthesia was present to level of the second rib. Lower extremities were completely paralyzed for two hours. Both the mother and child fully recovered. We assume that a massive spinal injection was given. Failure to obtain spinal fluid on aspiration is to be explained by the probable collapse of the membranes around the needle point upon attempts to aspirate.

The percentage of successful analgesia was 96 per cent in the 1,925 cases. We considered a caudal block successful if it was not necessary to add additional anesthetic agents.

Indications

We have used caudal block more or less as a routine measure in obstetric cases at this hospital. We have maintained a very strict list of contraindications, which will be given later. There are conditions in obstetrics in which caudal block is probably the anesthetic agent of choice. These conditions are: premature labor, heart disease, and pulmonary disease. There are times also when it is most desirable in toxemias of pregnancy, soft-part dystocia, and cesarean sections.

Contraindications

We believe that caudal block should not be carried out in surroundings lacking adequate materials and personnel to combat every possible type of accident. It should not be used in the case of hypertonic, hysterical, or unco-operative patients, and those not desiring it. It should not be used in patients with severe anemia or those bordering on exhaustion; likewise, not in those patients with abruptio placentae or placenta previa; nor in any case where the diagnosis is uncertain or where disproportion is suspected. If the patient gives a history of idiosyncrasy to the anesthetic agent; any deformity of the spine; or if there is any evidence of pyoderma, again its use should be avoided. This list does not necessarily include all the conditions which would prevent its use. More experience with it will probably bring some new ones.

Complications

Subdural Injection.—It is a definite contraindication to administer a caudal block if spinal fluid is aspirated before the injection or during the injection of the anesthetic fluid. This is one of our potentially most dangerous accidents and should be carefully guarded against. In our series of 1,925 cases, we knowingly aspirated spinal fluid in four cases.

Intravenous Injection.—If free blood is aspirated repeatedly, the attempts at caudal block should be stopped. Ordinarily, one can turn the needle, readjust it, wait two or three minutes, test again, and inject if no blood is aspirated.

Blood Pressure Drops.—Prophylaxis is most important in the selection of your cases; however, if blood pressure drop does occur, elevation of the lower extremities and the use of ephedrine sulfate will usually combat it successfully.

Infection.—Infection may occur as a subcutaneous abscess, osteomyelitis, epidural abscess, meningitis, septicemia, or as a simple skin lesion. Treatment consists for the most part of prophylaxis. Absolute sterile technique is essential.

Broken Needles.—One should not give caudal block if he is not familiar with the bony landmarks and technique. The regular 20 gauge flexible spinal needle, which we use, is quite safe. Never insert the needle to the hub, nor put on undue strain. The patient is always cautioned to lie still.

Comment

Repeated single caudal blocks for analgesia and delivery, using $\frac{1}{4}$ per cent tetracaine with small amounts of adrenalin added, has shown much promise in the small series of 152 cases. We intend to continue this type of analgesia until we can draw more abstract and useful deductions from its use. We feel that this form of analgesia is more advantageous than continuous caudal block for the following reasons:

The average length of labor under continuous caudal analgesia in a total of around 10,000 cases has been shown in primiparas to be between six and eight hours. In multiparas the average length of labor under similar conditions is around two hours. The average length of analgesia we obtained with single caudal injections with $\frac{1}{4}$ per cent tetracaine was two to three hours. The average number of caudal blocks that it was necessary to give in our series was less than three. Therefore, we feel it more advantageous to give one, two, or three single caudal blocks for complete analgesia and delivery than to use the continuous caudal.

Hingson² and Hodges³ and others have written that continuous caudal analgesia when carried out for periods of over seven to eight hours becomes increasingly more unsatisfactory, with complications increasing rapidly. We can administer two, and at the most three, single caudal blocks which will produce caudal analgesia for seven to eight hours. The complicated continuous caudal technique is not necessary.

Continuous caudal analgesia requires the constant attendance of the obstetrician or trained anesthetist, as we very definitely feel this responsibility should not be placed on a nurse. Single caudal blocks do not require this constant attendance, if the obstetrician is readily available.

Economically, a trained anesthetist must charge a large fee to attend an obstetric patient for six to eight hours checking the continuous caudal. Single caudal blocks can be given in three minutes. We must be practical in our attitude if we expect caudal block to be used extensively.

The patient can move at will with single caudal block. Examinations of all kinds can be made with ease, while under continuous caudal they are much more difficult.

The chances for infection are much less with single caudal block. One can maintain a very aseptic technique for three to five minutes, but for eight hours it is more difficult. There is a constant avenue for bacteria to the epidural space with the continuous caudal technique. We feel that merely covering the tray with a sterile towel and using care not to touch the barrel of the syringe is not enough to prevent infection.

The chances for broken needles are much less with single caudal blocks. Hingson and Edwards⁴ in an earlier report listed twelve broken needles in a series of six hundred cases. Lyons and Hansen⁵ report four broken needles, of the latest type, in their series of two hundred obstetric cases in which continuous caudal analgesia was used. We have not had a broken needle in 1,925 cases.

The chances for massive subdural injections are much less with single caudals. We never insert the needle deeper than is necessary to enter the caudal

canal, while in the continuous setup the needle must be inserted to the hub in every case. With the needle in place for several hours and the patient moving about, perforation of the dura or blood vessel could easily occur, with a serious accident resulting on subsequent injections.

It is much easier technically to insert an ordinary steel spinal needle into the caudal canal than the malleable ones used in the continuous caudal.

Backache is a very common complaint in those patients receiving continuous caudal. About 8 per cent of our patients complained of transitory sacral discomfort.

One-sided analgesia is very seldom seen with repeated single caudal blocks. The patient can lie flat on her back or turn as she wills. Often with continuous caudal, the patient will have a level of anesthesia on the dependent side with continuous cramps on the upper side.

The continuous caudal equipment is quite difficult to manage when the patient is being moved. A long tube protrudes from the back of the patient. One must be careful not to pull on that tube the slightest as the needle will be displaced or the tubing pulled from the needle hub. The accompanying tray of bottles, syringes, etc., which one must keep sterile, is difficult to manage for eight hours.

No special equipment is needed for single caudal blocks. The equipment for continuous analgesia is inexpensive, but is quite prone to become defective with use. Any well-supplied hospital will have the material necessary for single caudal blocks.

Summary

We have presented the results obtained in a series of 1,925 cases with caudal block. A technique for complete analgesia and delivery under repeated single caudal injections with $\frac{1}{4}$ per cent tetracaine has been described. This technique has been compared with continuous caudal analgesia, as advocated by Hingson and Edwards.

Conclusions

1. Single caudal block technique has a definite place in the practice of obstetrics. Its use is varied. It can be used as a single block for delivery or it can be repeated throughout labor for analgesia and delivery. Our results with caudal anesthesia for obstetric surgery are very encouraging.

2. Single caudal block, when given by an experienced individual under proper conditions, can be as safe or more so than other forms of analgesia.

3. Caudal block administered correctly will give as good results as any other form of analgesia.

4. The use of interrupted single caudal blocks for analgesia and delivery gives promise of effectiveness and safety for mother and child.

5. Caudal anesthesia in obstetrics should be limited to well-equipped institutions, which have a full-time resident or a teaching staff.

References

1. Hingson, R. A., and Edwards, W. B.: *J. A. M. A.* 123: 538, 1943.
2. Hingson, R. A.: *AM. J. OBST. & GYNEC.* 47: 718, 1944.
3. Hodges, W. R.: *J. A. M. A.* 125: 336, 1944.
4. Hingson, R. A., and Edwards, W. B.: *Anesthesiology* 4: 181, 1943.
5. Lyons, H., and Hansen, F. M., Jr.: *AM. J. OBST. & GYNEC.* 47: 105, 1944.

CONTINUOUS CAUDAL ANALGESIA IN OBSTETRICS ON TRIAL*

ROY E. NICODEMUS, M.D., F.A.C.S., LEROY F. RITMILLER, M.D., AND
LEWIS J. LEDDEN, M.D., DANVILLE, PA.

(From the Department of Obstetrics, Geisinger Memorial Hospital)

IN THE past two years numerous claims and counterclaims have been made for continuous caudal analgesia in obstetrics. In our opinion a fair analysis of this new method can be determined only if it is judged by the same standard as other types of analgesia.

We were one of the first groups to become interested in this new method and, consequently, received instruction in the technique as devised by Hingson and Edwards in the first course conducted at the Philadelphia Lying-In Hospital.

At the Geisinger Memorial Hospital we have endeavored for the past fifteen years to give adequate relief for pain in childbirth. This has entailed the use of numerous methods, always with the idea in mind of giving maximum relief of pain, consistent with safety to both mother and child.

We selected for this comparative study the last 500 consecutive deliveries prior to the institution of caudal analgesia, and the first 500 consecutive cases managed with continuous caudal analgesia.

In our clinic, which operates with a full-time staff in group practice, three physicians devote full time to the handling of all obstetric cases admitted to the hospital. We felt, therefore, that a fair and honest study comparing continuous caudal analgesia with other methods previously used would be enlightening and of some significance, especially since it correlates the results in 1,000 consecutive deliveries managed only by the Obstetrician-in-Chief and his two associates in a period less than two years.

For the sake of brevity in the remainder of this discussion the 500 consecutive deliveries prior to the use of caudal analgesia will be designated as Group I. All of these cases received sedation in the form of sodium pentobarbital in the amount of $4\frac{1}{2}$ to $7\frac{1}{2}$ grains. In addition, those cases requiring stronger sedation were given an oil ether mixture by rectum, and in all instances inhalations of ethylene or nitrous oxide were given at the actual time of delivery and repair.

The other 500 consecutive deliveries receiving caudal analgesia will be spoken of as Group II.

According to Table I it will be noted that the incidence of primiparas and multiparas in the two groups is almost identical, which is especially advantageous from the standpoint of comparison.

It was our impression before attempting this analysis that labors conducted under caudal analgesia were shorter in duration. Our figures in Table II have disproved this, and instead we have found that the average length of labor in primiparas in Group II was approximately one hour longer than in Group I; likewise in multiparas we discovered that labors in Group II averaged two hours longer than in Group I.

*Presented before a meeting of the Philadelphia Obstetrical Society, Dec. 7, 1944.

TABLE I. PARITY

PARA	GROUP I	GROUP II
Primipara	222	224
Multipara	278	276
Total	500	500

It may be asked by some: Why use a technique that tends to lengthen labor? Our reply is that it probably is a minor disadvantage if time is the unit of measure in obstetrics, but the strange part is we were convinced caudal labors were shorter until our figures proved otherwise, and the reason we thought they were shorter was that the patient was awake, comfortable, pleasant, and cooperative. It is when a patient is restless, uncoordinated, and irrational from her medication that the hours seem endless to the attending doctor and nurses.

TABLE II. AVERAGE DURATION OF LABOR

PARA	GROUP I	GROUP II
<i>Primipara</i>		
1st Stage	8 hr. 56 min.	9 hr. 34 min.
2nd Stage	1 hr. 34 min.	1 hr. 56 min.
3rd Stage	3 min.	3 min.
Total	10 hr. 33 min.	11 hr. 33 min.
<i>Multipara</i>		
1st Stage	5 hr. 59 min.	7 hr. 15 min.
2nd Stage	46 min.	1 hr. 26 min.
3rd Stage	4 min.	3 min.
Total	6 hr. 49 min.	8 hr. 44 min.

Let us now consider the incidence and results of occiput posterior positions in these two groups. In Group I a diagnosis of occiput posterior was made 94 times as against 122 times in Group II. Our study shows that spontaneous rotation took place in 86 out of 94 cases in Group I, or in 91.5 per cent, whereas only 69 rotated spontaneously out of a possible 122 in Group II, an incidence of 56 per cent. This, we believe, can be accounted for on the basis of diminished intensity of uterine contractions and relaxed birth canal where caudal technique is employed. It is, we believe, an accepted fact that strong uterine contractions forcing the vertex down against a resistant pelvic floor is the greatest aid to spontaneous rotation. Therefore, when these factors are altered we must expect the reverse to be true, and consequently, as shown in Table III, in Group I assistance to correct occiput posteriors had to be carried out in only 8.5 per cent of the cases as compared with 43.5 per cent in Group II.

In comparing Groups I and II as to types of delivery in Table IV, it is quite evident that the incidence of operative delivery is greatly increased where caudal analgesia is used. Our figures show that spontaneous delivery occurred 113 more times in the group in which caudal analgesia was not used; also low-forceps delivery was resorted to 103 more times with caudal analgesia. Midforceps delivery in the two groups showed the greatest contrast with twenty such deliveries under caudal analgesia as against three in Group I. This rather

TABLE III. OCCIPUT POSTERIOR

OCCIPUT POSTERIOR	GROUP I		GROUP II	
	(NO.)	(%)	(NO.)	(%)
Spontaneous rotation	86	91.5	69	56.5
Forceps rotation	5	5.3	20	16.5
Manual rotation	3	3.2	33	27.0
Total	94	18.8	122	24.4

marked increased incidence of operative deliveries with caudal analgesia, to our minds, indicates that the force of the uterine contractions are reduced in intensity; also, the expulsive force of the abdominal musculature is lost where this technique is employed. At the same time, it cannot be said to be a condemnation of the method, for in its favor we have a greater relaxation of the pelvic floor resulting in much less permanent trauma to these tissues. The shock of delivery is almost negligible and the blood loss is insignificant, all of which are major factors in the consideration of the patient.

TABLE IV. TYPES OF DELIVERY

TYPE	GROUP I		GROUP II	
	(NO.)	(%)	(NO.)	(%)
Spontaneous	312	62.0	199	39.2
Low forceps	160	31.8	263	52.0
Midforceps	3	0.6	20	3.9
Breech	28	5.6	25	4.9
Total	503		507	
	(3 sets of twins)		(7 sets of twins)	

We would like to call attention at this point to the ease with which breech deliveries were accomplished under caudal analgesia as compared with other types of anesthesia we have used. It is an established fact that breech deliveries have always carried a much higher mortality for the baby than almost any other type of delivery, largely because of the rigidity of the pelvic floor musculature preventing the necessary rapid delivery of the infant before asphyxia occurs. All these difficulties are overcome where caudal analgesia is employed since the soft tissues of the birth canal are so completely relaxed that they offer almost no resistance to extraction of either the breech or the head and this is all accomplished without placing the patient under deep surgical anesthesia.

TABLE V. FETAL COMPLICATIONS

COMPLICATIONS	GROUP I	GROUP II
Apnea—lasting a few minutes	102	10
Stillbirths	13	5
Neonatal deaths		
a. Full-term	2	1
b. Premature	5	6
Total	122	22

In Table V we have a notable contrast in fetal complications, especially marked in apnea lasting a few minutes after birth. This was found to be ten times more common in Group I where the barbiturates and rectal ether were used, necessitating resuscitation with oxygen in a fair percentage of cases. In Group II apnea and resuscitation were negligible factors since caudal analgesia has no effect upon the respiratory center of the baby. Again a notable factor was the much higher incidence of stillbirths in Group I as compared with Group II. This, we feel, can be explained on the basis of too intense and too frequent uterine contractions in Group I, occasionally resulting in intrauterine asphyxia of the baby, whereas in Group II we have already acknowledged that uterine contractions are of less intensity under caudal analgesia. Under the heading of neonatal deaths it is noted that there were seven in each group, which offers no point for comparison or discussion.

Probably the most important thing to consider in the use of any new procedure in obstetrics is whether or not the incidence of maternal mortality and morbidity can be reduced. In our series as shown in Table VI we had thirty-

seven cases of morbidity in Group I or an incidence of 7.4 per cent as compared with twenty-nine cases or 5.8 per cent in Group II. In neither group were there any mortalities. The margin of difference in morbidities in the two groups is small, yet we feel it is great enough to be of some significance. When we consider that operative procedures were 58 per cent more frequent in Group II where caudal analgesia was used, it becomes evident that we may have to revise our opinion that morbidity and mortality are proportionate to the incidence of operative interference in obstetrics. There are, we believe, certain other factors, such as minimal blood loss, absence of anesthetic shock, and prompt postpartum response of the patient as shown by immediate ability to ingest food and fluids, all of which tend to offset the increased hazards of operative procedures.

TABLE VI. MORBIDITY AND MORTALITY

	MATERNAL MORBIDITY	MATERNAL MORTALITY
Group I	37	0
Group II	29	0

In the discussion of analgesia for the obstetric patient, one's chief concern is the extent of relief of pain to that particular individual in her labor. It is to the best interests of each one of us for the patient to be able to say that she did not suffer long hours of pain and exhaustion, and yet we have all experienced the humiliation of having given some medication that we felt quite sure would give the desired good effect, only to find that the patient's reaction was entirely contradictory.

In our series we were unable to evaluate Group I concisely as to the percentage of good relief simply because a large portion of cases receiving barbiturates and rectal ether are uncooperative for hours due to narcosis. Even though they are not interrogated as to their relief of pain until the day after delivery, they often cannot differentiate between adequate and inadequate relief.

In Group II we have an entirely different standard by which to judge. The patient's sensorium is not affected; she is completely and entirely conscious at all times so that she is able and willing to give full cooperation throughout the entire labor and delivery. Consequently, our figures show that in the 500 cases delivered with caudal analgesia 469 had complete relief, 16 had partial relief, and 15 were failures. In other words, 93.8 per cent of this group had total analgesia, 3.2 per cent had only partial relief, and 3 per cent had none. Therefore, in our experience, to date, caudal analgesia has given a higher percentage of complete relief to the mother than any other method or combination of methods we have employed.

To some of you it may seem facetious to mention the morale and dispositions of the various personnel in the obstetric department. Yet, in all truthfulness, we can attest to the fact that this is true and of considerable importance. The nurses in the labor rooms enjoy caring for the caudal analgesia patients, whereas in other types of analgesia they are often harassed and exhausted trying to manage a restless, boisterous, uncooperative type of patient through her labor. Then, too, it is not necessary to hurry about trying to locate or call an anesthetist to control the patient for the final delivery and repair. No other anesthesia is required. The patient is simply moved to the delivery table at the proper time, delivered, and repaired if necessary while carrying on a pleasant conversation. Such conditions are bound to improve the dispositions not only of the nurses but of the doctors as well.

Still another fact well worth discussing and one which was mentioned earlier in the paper is the improved postpartum response of the patient receiving caudal analgesia. These patients are nearly always ready to eat a little food and drink fluids immediately after delivery, in fact many of them are able to do so during the course of their labor, all of which aids greatly in maintaining normal blood chemistry and consequently fluid and nutritional balance.

By reason of this prompt postpartum response, the patient may be moved to her room within a few minutes of the time of her delivery. The husband is amazed that he may see his wife so soon and delighted when he sees that she is awake, responsive, and happy, and apparently none the worse for her experience.

It is not enough to say that the method is too dangerous because of possible needle breakage, infection, penetration of the subarachnoid space, etc. We had no needle breakage in our series. One patient did develop a cellulitis superficial to the sacrum which accounted for one of our morbidities, but she made a complete recovery without complication. The subarachnoid space was penetrated in three different instances in the series, but this was promptly recognized and the procedure was discontinued: It is not a foolproof technique, but, on the contrary, one that needs careful thought and judgment and a willingness on the part of the doctor to remain close to the patient.

Summary and Conclusions

To summarize, we must in all honesty point out that our analysis shows that where caudal analgesia is used the labors are longer. Uterine contractions are of less intensity, the expulsive force of the abdominal musculature is lost. Occiput posterior positions rotate less often, and operative deliveries are increased. On the other side of the scales we can place the advantages of this technique, such as easier and safer breech deliveries, a lower incidence of stillbirths, a lower maternal morbidity, diminished blood loss with delivery, less permanent damage to the birth canal, and a pleasant, happy, cooperative patient. In other words, we have not yet found the utopian type of obstetric analgesia, but we are convinced that continuous caudal analgesia is a distinct advance in this field and an excellent method to add to the armamentarium of every obstetrician.

Discussion

DR. ROBERT A. HINGSON, PHILADELPHIA, PA.—Continuous caudal analgesia should be put on trial by all obstetricians who still manage women in pain throughout labor and delivery. It is not a technique of any two physicians or of Philadelphia physicians, but a procedure that has been developed through step-by-step progress of physicians from many parts of the world. It represents a frontal attack against the site of origin of obstetric pain itself. In many instances it eliminates the need for the "smoke-screen" of anesthesia and amnesia from anesthetic and narcotic drugs with which physicians have attempted to control pain.

As Dr. Nicodemus has pointed out, continuous caudal analgesia can prolong labor. I have seen it stop the processes of labor. By frank discussion of such disadvantages, we can protect both the patient and the baby from its misapplication. On the other hand, we have seen cases in which labor was accelerated by the use of this method.

Dr. Nicodemus did not indicate the upper level of analgesia in those cases in which he attributed the prolonged labor to caudal analgesia. Our observations have been that the forces of labor are impaired and eventually made ineffectual in prolonged high caudal blocks above the segmental levels of thoracic 8. Ideally, caudal block should not extend above the umbilicus (T-10). Nevertheless, on some occasions, unexpected high caudal block results from the average dosage of 30 c.c.

The revealing comparison of the improved condition of the baby managed with caudal analgesia should lead us to conclude that this method of pain relief is an indicated one even though it be an imposition on the physician's time.

During the past two years, 600 physicians have come to Philadelphia from all parts of the world to observe our technique of continuous caudal and, later, continuous spinal analgesia. Recently we sent questionnaires to these physicians and they reported the management of 46,000 labors and deliveries under this technique.

This altered obstetrics has presented a sociologic problem which demands attention both by physicians and by hospital authorities. It is an obstetric, as well as an anesthesiologic problem. We think the paper of Dr. Nicodemus is a landmark along the way which points toward adequate analgesia and pain relief in obstetrics even though physicians lose sleep in bringing about this effect.

DR. THADDEUS L. MONTGOMERY, PHILADELPHIA, PA.—Dr. Nicodemus has pointed out several advantages of the caudal method over the barbituric acid analgesia which he had formerly used. These, in respect to the lack of depression of maternal or fetal respiration, and in respect to greater relief of the mother, are generally accepted. I was a little disappointed that so little was said of the difficulties of insertion and administration of the caudal anesthesia, and nothing of the sequelae of caudal anesthesia. Most of those who have given even a few caudal anesthetics, even after careful instruction by competent anesthetists, have experienced some difficulties. Not a few patients have returned following caudal anesthesia with some local complaint.

Aside from the technical difficulties, and the complications of minor or moderate severity, the crux of the situation seems to lie in the problem of how far we can go with any method of anesthesia in obstetrics which inhibits the natural powers of labor. Certainly, thus far, no satisfactory substitute has been found for the natural fashion of delivery, including the dilatation of the cervix by recurrent contractions of the uterus in the first stage, and propulsion of the fetus through the birth canal by the combined efforts of the uterus and abdominal muscles in the second stage. The longer I am in obstetric practice, the more impressed I am with the favorable condition of mother and child after a so-called natural labor, and with the fact that the earlier we interfere in the mechanism of labor, the greater are the complications that will result.

When we began using so-called prophylactic forceps, we applied them only when the scalp was visible and the perineum and vulva were projected forward in front of the advancing head which had molded itself into the outlet of the pelvis. Year after year we seem to be interfering somewhat earlier in this mechanism. Now, with the advent of caudal anesthesia and of spinal anesthesia in obstetrics, we rather impertinently apply our forceps with the head in midpelvis, or in low pelvis, and complete in a few minutes what Nature ordinarily takes an hour or two to accomplish. That such procedures can be done consistently even by competent obstetricians, without unnecessary damage to the mother or to the baby, is not possible to believe.

I feel quite in agreement with the opinion that the regional methods of anesthesia, that is, spinal, caudal, and local, offer many advantages over central or systemic anesthesia. The greatest of these, of course, is the lack of anoxemia in the baby and the freedom from inhalation anesthetic accidents in the mother. In these directions, the regional methods of anesthesia represent quite a step forward. It would appear also that the more peripherally administered the anesthesia, the safer the effects. In this direction, therefore, the injection of a local anesthetic agent in the perineum during the final stage of delivery and for the repair of episiotomy, combined with "whiffs" of nitrous oxide and oxygen or ether, is one of the very safest of anesthetic methods, and one which has achieved and should continue to receive a large following in obstetric practice.

Some months ago, from the material of our clinic at the Temple University Hospital we presented a comparative study of caudal and spinal anesthesia in obstetric practice. We found that each of these two methods presented certain advantages and certain disadvantages. The spinal method was administered more readily and more certainly, and with a higher degree of success. It seemed somewhat safer in that we had comparatively little reaction and the anesthesia was always given in the delivery room when the entire personnel for delivery, including doctors, anesthetists, residents, and nurses, was present. It was given over only a comparatively short period of time, so that close observation was necessary for only an hour, or an hour and a half. In some few cases, however, the spinal anesthesia was followed by a

moderate postpartum bleeding, and in no case did the anesthesia appear to have as profound a relaxing effect on the pelvic floor and perineum as did the caudal anesthesia.

There was one detrimental feature, however, which was common to both methods. All sense of perineal pressure was obtunded, and the head never advanced beyond the pelvic floor unless the patient was consistently and continuously coached to bear down. Even then a spontaneous delivery was only accomplished in the multiparous patient. In a number of cases we found ourselves doing so-called low forceps delivery, which was anything but a simple extraction of the fetal head through the vulva. As has recently been mentioned by Baptisti, many of the forceps necessitated drawing the head down beneath the symphysis pubis and dilating the pelvic floor and perineum with rather strenuous traction. This, we feel, is not good obstetrics. I am inclined to believe that anyone who uses either the caudal or the spinal anesthetic method, and who analyzes his cases honestly, will acknowledge that there are quite a few deliveries of this type.

DR. W. ROYCE HODGES, CUMBERLAND, MD.—Our work is done in a general hospital with no interns or residents. Nevertheless, since Oct. 3, 1942, over 500 obstetric cases have been delivered under continuous caudal analgesia. We have also used continuous spinal anesthesia in all forms of operative work, in abdominal and pelvic surgery, and favor it. Under the circumstances in which we are forced to work, however, I feel that continuous spinal analgesia must be limited to those few obstetric patients who cannot for some reason be given continuous caudal analgesia.

When using continuous caudal for pain relief in our labor cases, the patients are under constant observation by one of three graduate nurses who have been trained by us. With these nurses in attendance we feel perfectly safe in leaving these patients throughout the remainder of their labor, it being understood that we are constantly on immediate call. Our successful results have been in direct proportion to the proper placing of the caudal needle. Of our first 300 cases, 222 were completely satisfactory. Forty-two of the remaining 78 cases were classified as failures, and by far the majority of this group failed because of faulty insertion of the needle. Of the remaining 36 patients, in the light of our more recent experience, at least half were due to failure to insert the needle properly. In short, most of our disappointments with the method have been due not to any faulty principle of the method, but to personal failure in technique.

Another pitfall which we are learning to avoid through experience is that of too early administration. In primiparas especially, if one waits until the patient is crying for relief of pain after the administration of an average dose of the usual barbiturate, or a small early dose of morphine or demerol, providing there is progressive dilatation of the cervix and descent of the presenting part, then is the time that continuous caudal analgesia can be expected to give ideal results. From the standpoint of time, continuous caudal of four to five hours' duration in primipara has been the maximum optimum time for our patients. We have had patients carried over a period of seven to twelve hours and longer with good result, but this is not the rule.

One other point is that our experience in the increase of operative deliveries is very similar to that of Dr. Nicodemus. I know that I have been responsible for the death of two babies because of faulty judgment in trying to rotate the head too soon. At the present time my feeling is that if a persistent posterior head offers too much difficulty in manual or instrumental rotation, it is wiser for me to let up on the caudal, allow the patient to bear down with her returning pain, and in this manner greatly aid in the rotation.

To condemn this method because of a few personal failures is more than unfair. In our hands, under entirely different circumstances from which others work, we find it a very favorable method and we will continue to use it until we find something better.

DR. NICODEMUS (closing).—In regard to the question that Dr. Montgomery brought out, I can only say that I know of no sequelae in our series following the use of caudal. We do feel, however, that within a few hours after delivery the patients are likely to develop over-distended bladders due to the fact that they have not regained the sensation in this region. Hence we make it a point to have our nurses inspect the abdomen frequently after delivery and catheterize one or more times during the first twelve to twenty-four hours when necessary.

What has been said about nursing requirements is very true, but I think as time goes on more doctors will be available and the hospitals will again have adequate nursing service. However, I see no reason why a resident trained in this particular method could not be called upon to give the caudal analgesia at the proper time in labor. We do it in our institution and it works very satisfactorily.

THE USE OF FINE CHROMIC CATGUT FOR POSTPARTUM PERINEAL REPAIR*

EDWARD G. WATERS, M.D., F.A.C.S., JERSEY CITY, N. J.

(From the Margaret Hague Maternity Hospital)

THIS is a record of experiences with perineotomy repairs using very fine chromic catgut sutures. The number of cases providing the data is sufficiently large and carefully followed to permit a statistical appraisal of the material, and other data experimentally obtained are pertinent. While the primary object is to observe tissue reaction and healing and the patient's pain response to the very fine suture used, due recognition is given the varied factors which act in any delivery as agents influencing perineal repair and healing. Very fine catgut sutures are not commonly used for postpartum repairs of birth tract injuries or incisions although the literature of the past few years indicates a growing awareness of its value in surgical technique.

While an exhaustive exposition of the principles indicating the use of very fine catgut material is not proposed here, a consideration of present-day types of fine chromic sutures as compared to former and older brands is certainly in order.

The function of a suture is to obtain hemostasis and hold in apposition the divided structures sufficiently long to permit adequate wound healing before loss of effective suture strength through absorption. Catgut is mainly collagen prepared from the submucosa of the jejunum of the sheep. As natural or plain catgut, it has a fairly rapid rate of absorption and therefore is seldom applied except where rapid loss of strength is unimportant. To prolong the absorption time, these collagenous strands are chromicized and made uniform in smoothness and tensile strength. The storage solution must cause a minimal degree of tissue irritation.

An emplaced suture acts essentially as a foreign body and provokes the reaction one might expect. The dilatation of the capillaries and veins and polymorphonuclear leucocyte reaction; extravasation of plasma cells and plasma is to be expected. The action upon the suture is to soften it, fracture it, and prepare it for absorption. The enzymatic proteolysis from polymorph degeneration begins and the macrophages proceed to digest and phagocytose the strands. Since all of these processes interfere with the appearance and activity of fibroblasts, it is obvious that the most desirable suture is one which evokes the *least* leucocytic response and permits *earliest* proliferation of fibroblasts. In properly receptive tissues, at the end of a week the suture should be surrounded by new capillaries, young fibroblasts with developing collagenous fibers, a minimal number of leucocytes, and yet retain some of its initially inherent tensile strength. Excessive tissue reaction with collection of serum, the onset of infection with increased numbers of leucocytes, cellular necrosis from lacerated or badly bruised wounds, contused and ecchymotic areas, all interfere with the physiologic process described. Many systemic disturbances, especially those associated with emaciation, starvation, general debility, diabetes, etc., interfere with wound healing. It has been experimentally determined that chromic

*Read before a meeting of the New York Obstetrical Society, Jan. 9, 1945.

catgut produces a lesser foreign body reaction than plain catgut and that smaller sizes of chromic catgut, while producing a minimal degree of tissue reaction, retain tensile strength proportionately much longer than larger sizes. A consideration of the available experimental data therefore indicates the *use of the smallest chromic sutures possible* with due consideration of the need for initial tissue coaptation. It has been demonstrated unquestionably that more closely applied sutures of smaller sizes give sounder wounds than those of large chromic catgut placed at greater intervals. One may therefore conclude that properly chromicized catgut of fine gauge is the correct material to use from a theoretic standpoint: first, because smaller-sized needles are used with resulting lesser damage to the punctured tissue; second, the mass of foreign material lodged in the wound is reduced; third, the knot mass is smaller; fourth, unfavorable tissue reaction is diminished, with prolongation of the effective tensile strength of the suture; fifth, there is less superfluous tensile strength in the finer chromic sutures which in itself provides an effective restraint upon strangulation of tissue by the operator.

All of these considerations designate a fine type of chromic suture material as the proper one to employ where absorbable sutures are to be placed in tissue, consistent with the local need for tissue approximation.

The chromic catgut material throughout the series reported in this paper was No. 0000 chromic catgut, the gauge of which is approximately standardized at 0.007 with average tensile strength of 2 pounds.

Experimental Data

At attempt was made to determine the frequency of suture fraying, rate of absorption, and residual tensile strength of strands of No. 0000 chromic catgut remaining in the perineal tissues three, four, five, six, and seven days. Several free strands were placed in non-lacerated perineums of patients and removed at intervals from the third to seventh days, to compare the effects upon the suture material over that period.

Reference to Fig. 1 shows the tensile strength of the suture material as determined immediately upon the withdrawal of the suture strands from the perineums of patients in whom they had been planted after normal spontaneous deliveries without perineotomies. Although more than 70 perineums were used, data could be recorded on few more than 40 individuals because of technical difficulties encountered. Many strands were removed during perineal care, during replacement of vulvar pads, and often by overattentive nurses, or the strand was retracted into the perineum and could not be recovered. However, 73 strands were recovered at varying times from 41 patients and subjected to examination and determination of tensile strength. It is notable that none of these strands showed any fraying on the third, fourth, or fifth days. Two strands showed fraying on the sixth day, and one showed marked fraying on the seventh.

The tensile strength in the strands removed on the third day varied from 1 pound 4 ounces to 2 pounds 8 ounces. On the fourth day the range was 1 pound 7 ounces to 2 pounds 10 ounces. On the fifth day, 1 pound 3 ounces to 2 pounds 12 ounces. On the sixth day, 1 pound 2 ounces to 2 pounds 1 ounce. On the seventh day, 1 pound 2 ounces to 2 pounds 3 ounces. The average tensile strength for all of the suture strands removed from the third to the seventh days is noted: 1 pound 14 ounces, 1 pound 15 ounces, 1 pound 10 ounces, 1 pound 8 ounces, 1 pound 8 ounces. In other words, there is only an average loss of 6 ounces tensile strength in the same suture material from the third to the seventh day in the postpartum perineum. It is apparent that, while the absorption rate may vary in different individuals, a fair constant may be obtained for any group. Varying individual factors make impossible unit predictions on the time length a given suture will retain ten-sile strength and resist absorption. But for any large group, an accurate appraisal can be made, especially for the early and all-important healing time. It is our belief that fraying of sutures is due largely to careless surgical handling, notably loop ties and suture injury with hemostats and needle holders. This is borne out by the rarity with which fraying was encountered in any of the experimentally placed strands.

The tissue reaction to varying sizes of chromic catgut is well seen in the four photomicrographs (Figs. 2 to 5). The size 0 medium chromic catgut and size 0000 medium chromic catgut were used for the comparative tests. Dogs were anesthetized with intravenous sodium pentobarbital and strands of chromic catgut material were imbedded in the anterior wall of the stomach. At the end of five days, sections were removed and paraffin block sections were obtained of the suture and the surrounding tissue and stained with hematoxylin eosin. A similar technique was carried out by removing the section of the stomach wall at the end of fourteen days when advanced healing was presumed to have occurred. Study of the section shows the absence of unfavorable tissue reaction about the 0000 strands with early fibroblastic formation. The absence of leucocytic infiltration is notable. In the sections removed at the end of fourteen days for microscopic examination, the size 0 or larger strand is noted to be markedly fractionized with approximately half of the strand absorbed. While fibroblastic infiltration is well advanced, it is not nearly so evident nor clear-cut as with the 0000 catgut where the strand shows no evidence of absorption, no tissue reaction other than active fibroblastic formation.

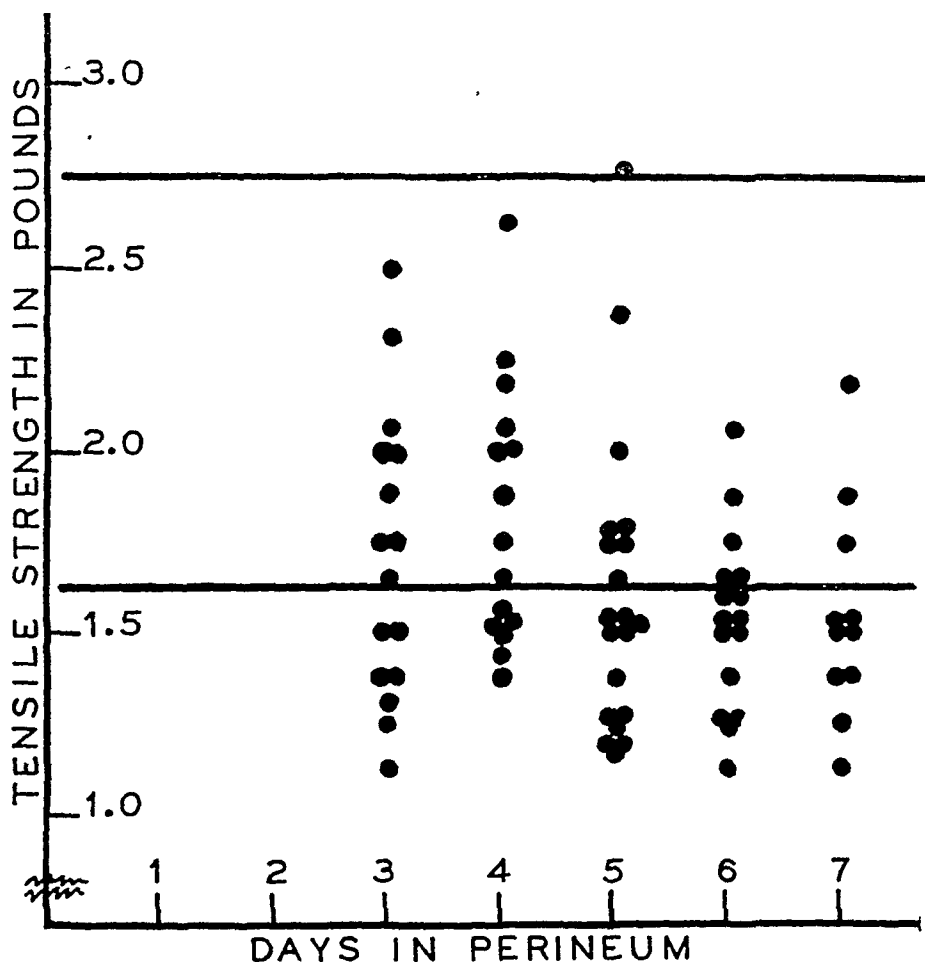


Fig. 1.

Analysis of Clinical Material

The perineal repairs and operations noted in the tables were made with No. 0000 chromic catgut threaded on fine needles. The technique commonly employed was a lock stitch on the mucosa and musculofascial coat of the vagina, and a continuous muscle-approximating suture in the perineum, terminating as a subdermal stitch. Occasionally an interrupted figure-of-eight suture was placed in the depth of the perineal body. When median perineotomies involved the sphincter, the latter with its fascial coat was approximated with two or three interrupted No. 0000 chromic sutures. Nonabsorbable sutures were not used in any instance.

Most of the tables are self-explanatory and require no further elaboration.

The preference for median perineotomy is apparent since it composes more than three-fourths of all the perineal incisions elected. It is well to note that the selection of median perineotomy is often dependent on the type of delivery anticipated as well as the anatomic character of the pelvic outlet and perineum itself.



Fig. 2.

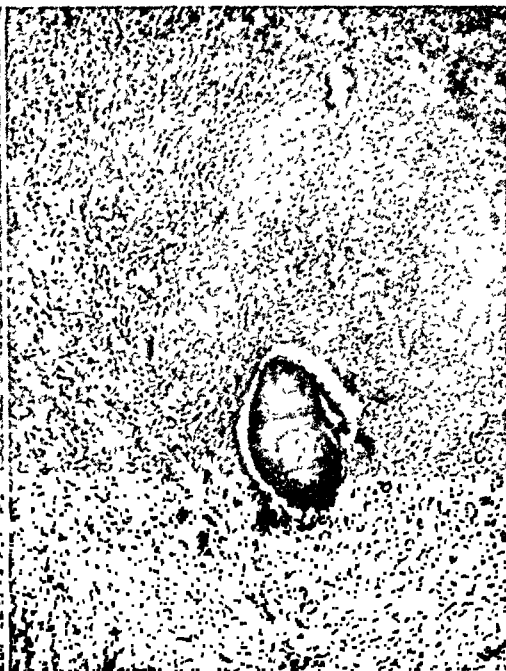


Fig. 3.

Fig. 2.—Size 0 medium chromic catgut embedded in the anterior wall of the stomach of the dog and sections removed for microscopic examination at the end of five days. No evidence of absorption of catgut. Leucocytic infiltration moderate. Early fibroblastic formation.

Fig. 3.—Size 0000 medium chromic catgut embedded in the anterior wall of the stomach of the dog and sections removed for microscopic examination at the end of five days. No evidence of absorption of strand. Leucocytic infiltration absent. Early fibroblastic formation. Note the proximity of intact strand to surrounding tissue. Compare the width of the tissue defect with that made by the 0 strand.

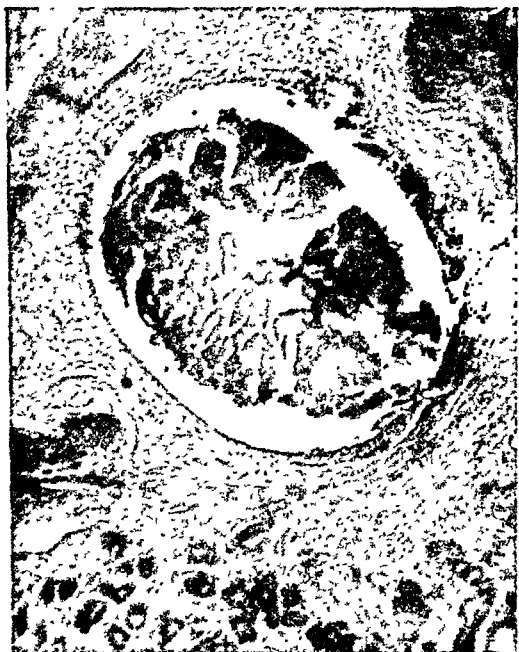


Fig. 4.

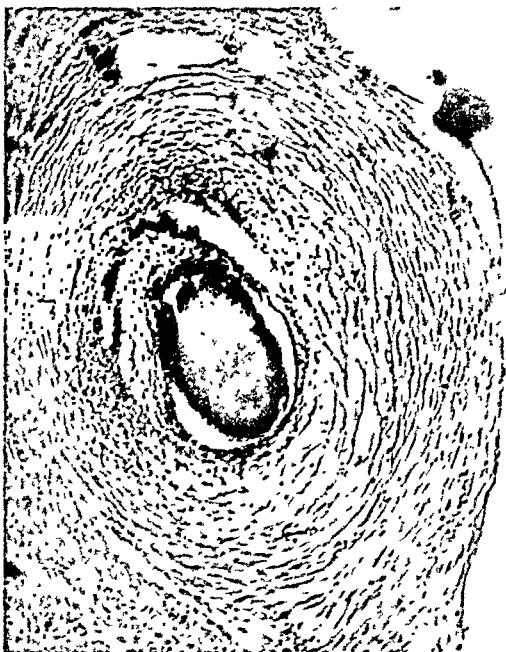


Fig. 5.

Fig. 4.—Size 0 medium chromic catgut embedded in the anterior wall of the stomach of the dog and sections removed for microscopic examination at the end of fourteen days. Fifty per cent of the strand is absorbed. Leucocytic infiltration normal. Fibroblastic infiltration well advanced.

Fig. 5.—Size 0000 medium chromic catgut embedded in the anterior wall of the stomach of the dog and sections removed for microscopic examination at the end of fourteen days. No evidence of absorption of catgut. Leucocytic infiltration absent. Fibroblastic infiltration well advanced.

TABLE I

Primiparas		243		61%	
Multiparas		157		39%	
Elderly primiparas		31		8%	
Previous stillbirths	One	14	cases 3.5 %}	4.25%	
	Two	3	cases 0.75%}		
Previous miscarriages	One	36	(17 had delivered living babies also)		
	Two	5			
	Three or more	4			
Previous cesareans		2			
Previous Manchester-Fothergill		2			
<i>Type of Perineal Injury</i>					
Median perineotomy		291	73.0%}	76%	
Median perineotomy with 3° extension		12	3.0%}		
Right mediolateral episiotomy		68	17.0%		
Median lacerations		26	6.5%		
<i>Length of Labor (Hours)</i>					
FIRST STAGE			SECOND STAGE		
1-6	175}	78%	0-4	328	82%
6-12	138}		4-6	22	
12-18	25		6-8	3	
18-24	12		Over 8	6	
Over 24	17				
<i>Anesthesia</i>					
Gas-oxygen + ether	269	67.0%	Spinal	67	17%
Ether	18	4.5%	Local block	39	10%
Miscellaneous	6		Intravenous	1	

TABLE II

TYPE OF DELIVERY	NO.	PER CENT
Normal spontaneous	212	53
Median perineotomy	165	41.2
Right mediolateral episiotomy	25	6.2
Median laceration	20	5.0
3° extension of median	2	0.5
Low forceps	135	34
Median perineotomy	96	24
Right mediolateral episiotomy	29	7.2
With laceration	2	0.5
3° extension median perineotomy	8	2.0
Midforceps	27	7
Median perineotomy	17	4.2
Mediolateral	10	2.5
Breech	14	3.5
Spontaneous with med. perineotomy	2	0.5
Forceps to aftercoming head— med. perineotomy	8	2.0
Right mediolateral episiotomy	4	1.0
Laceration	3	0.75
3° extension median perineotomy	2	0.5
Version and extraction (median perineotomy)	2	
Craniotomy (median laceration)	1	
Face presentation (median perineotomy)	1	
Twins	3 sets	
<i>POSTPARTUM OPERATIONS</i>		
Posterior colpoperineorrhaphy	32	8.0
Cystocele repair	2	0.5
Hemorrhoidectomy	4	1.0

TABLE III

COMPLICATIONS				
1. <i>Medical</i>				
Heart disease	3		Diabetes	3
Hyperthyroidism	1		Cholecystitis	1
Pneumonitis	1		Antepartum psychosis	1
2. <i>Surgical</i>				
Fibroids	6	8 or 2%	Hemorrhoids, infected	2
Fibroids with hemorrhage	2		Hemorrhoids, severe	6
Pelvic endometriosis	2		Ether conjunctivitis	1
Chronic mastoiditis	1			
3. <i>Obstetric</i>				
Placenta previa	4		Pre-eclampsia	2
Placental abruption	1		Eclampsia (intrapartum)	1
Adherent placenta	2		Sepsis (antepartum)	2
Postpartum hemorrhage	5		Mastitis	2
Postpartum bladder atony	1		Thrombophlebitis	2
Pyelocystitis	2		Polyhydramnios	1
Prolonged rupture of membranes	4			
4. <i>Incidental Complications</i>				
Sutures through rectum 2—not cut out, primary healing				
Rectum buttonholed with median incision 2—primary healing				
<i>Fetal Mortality</i> - - - - - Total 9 or 2.25%				
Autopsies obtained 8				
Dead before labor 3 { 1 monstrous				
2 habitual death of fetus in utero in same patient				
Dead during labor 3 { 1 congenital heart				
1 congenital heart in premature infant				
Neonatal deaths 3 { 1 premature with atelectasis, 26 weeks				
1 pneumonia at 3 weeks				
Weights of babies in third-degree extension of median perineotomy 6, 6-10, 6-10, 7-3, 7-3, 7-6, 7-12, 7-13, 8-1, 8-8, 8-12, 9-3				
<i>Sex</i>				
<i>Weights</i>				
Male	192	No significant difference		
Female	211	in weights of sexes		

TABLE IV.

PAIN RESPONSE*			NO.	PER CENT
No Pain			290	72.5
DURATION IN DAYS		NO.	TOTAL	PER CENT
Mild	1	11	64	16
	2	36		
	3	13		
	4	4		
Moderate	1	1	34	8.5
	2	21		
	3	7		
	4	4		
Severe	Over 4	1	10	2.5
	1	1		
	2	4		
	3	2		
	Over 3	3		

POSTPARTUM PERINEAL STATUS			
Primary healing		395	98.8
Stitch abscess (no gross infection— clean secondary healing)		3	
Gross infection (no resuture)		1	
Complete breakdown (3° extension)		1	
Fistula		0	
Labial hematoma (3 with local block)		4	

*No pain—complained of no pain. On question said there was none.

Mild—complained of no pain. On question admitted a soreness but no relief requested.

Moderate—complained of some pain or discomfort. No local treatment given or requested.

Severe—complained of severe pain, demanded relief, usually compresses or local treatment.

TABLE V. END RESULTS—FOUR TO SIX WEEKS POSTPARTUM

		NO.	PER CENT
Number of cases followed		321	80
Nulliparous-type introitus (too tight—7)			
Tight	64	96	30
Normal	32		
Lax	12		
Cystocele	1°	2°	3°
Primipara	5	0	0
Multipara	6	1	1
Rectocele	1°	0	0
Primipara	1	0	0
Multipara	4	0	0
Prolapse		2°	
Multipara		2	

Thirty-two multiparas presenting relaxed posterior walls had corrective postpartum operations. There were no complications in this group incident to the use of fine chromic suture material. Experiences with the patients suffering third-degree extensions indicate no valid reason for using nonabsorbable sutures in this group.

The *most significant results* in this study are to be found in patient pain response, the incidence of primary healing, the rarity of infection, and the end results as noted four to six weeks postpartum. In my experience with perineal incisions, lacerations, or operations, an incidence of over 72 per cent of patients with *no postoperative pain response* is notable. Many were multiparas who had previously had perineal repairs with other and heavier types of suture materials. Recent pain experiences should be most acute, yet with few exceptions such patients recorded discomfort and pain following former perineotomy as having been much more severe. Since pain is a subjective symptom which can be calibrated only by the sufferer, the pain response is charted in conformity to the explanatory key. This is as accurate a record as one may obtain, since the patient makes it herself.

The postpartum perineal status, however, is a different matter, for here we have objective findings permitting constant interpretation. Ninety-eight and eight-tenths per cent of these wounds healed by primary intention with no excessive or notable tissue disturbance. These included many in the moderate or severe pain groups. There was only one gross infection in the entire series and one complete breakdown. The latter occurred in a median perineotomy wound with third-degree extension which became grossly infected subsequent to the employment of local anesthesia. While we do not expect perineal infections to be commonly seen on any service in the hospital, a listing of three minor and two major perineal infections in a group of 400 patients is regarded as good.

Conclusions

The end results noted on the chart represent a follow-up of 80 per cent of the group studied. It suggests that the use of very fine chromic catgut sutures is followed by primary healing of the incised perineum. Further, when the soft parts are neither excessively over-stretched by the fetus nor damaged by instrumentation, a nulliparous type introitus may be looked for as the end result in most parturient patients. The results designate primary posterior colpoperineorrhaphy as a good procedure to follow in multiparas with relaxed structures.

It is our conviction that a consideration of the theory of wound healing, experimental data of others and in our own lesser efforts involving the use of fine chromic suture material and the clinical data derived from the study of 400 patients in whom this type of suture material was used, gives evidence to our belief that it is the proper suture material to use for postpartum perineal repairs.

I wish to express my thanks to Dr. Adeline Pendleton for assistance in the compilation of the experimental data. Also to Dr. R. Clock of Davis & Geck, Inc., for supplying the needed apparatus.

THE RH FACTOR IN OBSTETRICS*

JACOB HALPERIN, M.D., F.A.C.S., MENDEL JACOBI, M.D., F.A.C.P., AND
ALVIN DUBIN, B.A., BROOKLYN, N. Y.

*(From the Department of Obstetrics and Gynecology and the Department of Pathology
of the Beth-El Hospital)*

ENOUGH data and facts have by now been accumulated since the discovery of the Rh factor by Landsteiner and Wiener^{1, 2} and the subsequent work by Levine and coworkers³⁻⁶ to show the important relationship of erythroblastosis and the Rh factor, as well as the cause of most intragroup transfusion reactions in women who are pregnant, or who have recently delivered.

With this constantly accumulating evidence of the important role of the Rh factor in pregnancy, we decided to examine our histories to appraise the value of the routine determination of the Rh factor in all pregnant women. We reviewed all the obstetric cases in the maternity division of the Beth-El Hospital for a period of eighteen months, covering the entire year of 1943 and the first six months of 1944.

During this period of eighteen months, 3,885 women were delivered (Table I). These cases do not include pregnancies under four and one-half months' gestation. Up to that period they are not admitted to our obstetric department.

TABLE I. OBSTETRIC CASES REVIEWED FOR AN EIGHTEEN-MONTH PERIOD, 1943, TO
JUNE, 1944, BETH-EL HOSPITAL

Total number cases delivered		3,885
Stillbirths, all causes		94
	Males 55	
	Females 39	
Stillbirths, cause designated, but other than erythroblastosis		21
Stillbirths, cause unknown		73
	Males 46	
	Females 27	
Total number live births		3,791
Total number that developed jaundice or any form of erythroblastosis		40
	Males 26	
	Females 14	
Male-female ratio almost 2:1		

Of the 3,885 deliveries there were 94 stillbirths. Deducting from this number all traumatic deliveries, and those where the cause could be rather definitely assigned, such as toxemias, ablatio placenta, prolapsed cord, large fibroids numbering 21, there still remained 73 fetal deaths of unknown causes, ranging from five months' gestation to full term. Of the 94 stillbirths, 55 were males and 39 females. However, of the 73 unexplained deaths, 46 were males and 27 were females, giving a percentage of 63 per cent for males to 37 per cent for females. As the normal ratio of births in the hospital is about equal for both sexes, the uneven ratio in the stillbirths may be of significance. We shall refer to this again later in the paper.

Of the total number of 3,791 live births for the same period, 40 of the newborn infants developed erythroblastosis in some form, ranging from moderate jaundice to the most severe form, from which the baby ultimately died. This is slightly over 1 per cent. Twenty-six of these were males and 14 were females, a ratio of almost two to one.

*Read before the Brooklyn Gynecological Society, Oct. 6, 1944.

TABLE II. ANALYSIS OF ERYTHROBLASTOSIS DEATHS, 1943-1944, BETH-EL HOSPITAL

Total number deaths	18
Autopsies performed	10
	Males 9
	Females 1
Autopsies not performed	8
	Males 6
	Females 2
Total male-female ratio 5:1	

Ten of the male erythroblastotic babies died, a percentage of 40 per cent, while only one of the female erythroblastotic babies died, a percentage of 7 per cent, the ratio of male deaths over females being almost six to one (Table II). Of the eleven fatal cases, ten came to autopsy. Only in one of these cases was the mother Rh positive; all the rest were Rh negative. In this one case, the baby and the father were also Rh positive. The erythroblastosis in this case can be explained by the mother being type O, and the baby type A. Other investigators have had similar experiences with reference to erythroblastosis in cases in which both mother and baby have been Rh positive.^{7, 8}

This finding in erythroblastosis, that the proportion of males is far greater than females, and that the prognosis for a female recovering from erythroblastosis is much better than for a male, is a new phase.

That stillbirths of unknown cause were more frequent in males than females was not entirely new to us. For the past several years we have observed it clinically; but that the actual figures should be so striking was a surprise. We decided, therefore, to check with another source, and examine the records of another institution. Dr. Silik Polayes, attending pathologist of the Cumberland Hospital (Brooklyn), was kind enough to place his pathologic and clinical records at our disposal. We reviewed 103 of his cases with a clinical or autopsy diagnosis of erythroblastosis. Of this group of cases, 51 were from the Cumberland Hospital and 52 collected from various other sources. As the resultant findings were almost identical in both groups, we shall present the figures of both groups together (Table III).

Fifty-seven of the 103 cases of erythroblastosis died but did not come to autopsy; 43 of these were males and 14 females, a ratio of more than 3:1. On 13 stillbirths, autopsies were performed, and of these, 7 were males and 6 females, the proportion almost even; but in the autopsies of 17 neonatal deaths, there were 14 males, and 3 females, a ratio

TABLE III. ANALYSIS OF RECORDS OF ERYTHROBLASTOSIS CASES FROM THE CUMBERLAND HOSPITAL, PROSPECT HEIGHTS HOSPITAL, AND OTHER SOURCES

Number of case records analyzed	103
Clinically diagnosed, died, and not autopsied	57
	Males 43
	Females 14
Ratio of males to females	3:1
Autopsies performed	30
Autopsies on stillbirths	13
	Males 7
	Females 6
Autopsies on newborns that died during neonatal life	17
	Males 14
	Females 3
Ratio of males to females almost	5:1
Clinically Diagnosed Cases of Erythroblastosis that recovered	
	Total number 16
	Females 12
	Males 4
-Female-Male ratio (reversed)	3:1

*The case records were furnished through the courtesy of Dr. Silik Polayes, pathologist to the Cumberland and Prospect Heights Hospitals, Brooklyn, N. Y.

of almost 5:1. These figures coincide with our own findings. Only 16 of the 103 cases recovered, and it is noteworthy to point out that of the 16 cases, only 4 were males, exactly the reverse ratio. This suggests a greater severity of the disease when it occurs in the male, and the much greater chances for a female recovering from erythroblastosis than a male.

If in a still larger series of cases the same findings maintain, we would have to seek another factor to explain the greater severity of the disease in males. It is difficult to explain it on a sex-linkage basis. Wiener and Landsteiner² conclude from observation and study of families that the Rh factor is not sex linked, and that the distribution of it is the same in both sexes as well as in the four blood groups.

Research would probably have to be pursued with the thought in mind that there may be another genetic factor not yet known, which is sex linked.

Before we instituted the routine determination of the Rh factor in the obstetric department, one maternal mortality occurred due to a transfusion of Rh-positive blood to an Rh-negative patient, and one near fatality for the same reason. In the first instance a transfusion of 500 c.c. of properly typed and cross-matched blood was given, without immediate reaction, to a multipara who was admitted because of placenta previa and bleeding. A cesarean section was performed. She delivered a male with erythroblastosis. Subsequently the Rh factor in the mother was found to be negative. She ran a course similar to acute nephritis, developed uremia, and despite all efforts died on the twelfth day. The second case was a primipara who was delivered with forceps and suffered lacerations with profuse bleeding. Plasma was administered on the delivery table; the next day she was given a transfusion of 800 c.c. of whole blood, properly typed and cross-matched. She had an immediate and severe reaction with constricting pain in the chest. The erythrocyte count next day was 1,250,000, with a hemoglobin of 28 per cent. Nitrogen retention products appeared in the blood. An Rh factor determination showed her to be negative. Subsequent transfusions were given with Rh-negative blood and the patient recovered.

In view of the literature being so replete with pertinent facts concerning the Rh factor in obstetrics, and the accumulated evidence of our own investigation, our obstetric department early this year inaugurated the routine typing and determination of the Rh factor in all women attending our prenatal clinic, and urged all members of the staff to do likewise on their private patients.

The following is an analysis of the first consecutive 500 obstetric patients on whom the Rh factor was determined (Table IV). Where the Rh factor

TABLE IV. ANALYSIS OF 500 CONSECUTIVE PRENATAL RH FACTOR DETERMINATIONS IN PREGNANT WOMEN AT THE BETH-EL HOSPITAL

Total number obstetric cases delivered	500
Rh positive	434
Rh negative	66
Incidence of Rh-negative cases	13.2%
Incidence of erythroblastosis in the newborn delivered of Rh-negative mothers:	
Number of cases delivered	35
Stillbirths and those newborns that developed erythroblastosis	23
Incidence	65.7%
Stillbirths	5
Neonatal deaths	2
Males 6 Females 1	
Male-female ratio	6:1
Cases still undelivered	31

was found to be negative the factor was also determined in the husband when possible.

Of the 500 consecutive determinations we found 66 Rh-negative women, an incidence of 13.2 per cent. This percentage is within the range of other investigators.^{12, 13}

To date, 35 of the 66 Rh-negative women have been delivered, and, of these, 23 showed some form of erythroblastosis symptoms. This represents 65.7 per cent of the total Rh-negative patients.

Males again predominated in these erythroblastotic newborn infants, 18 being males and 5 females. Not only were the males predominant, but they represented the most severe types. Four of the male infants died, but none of the females. These findings are in complete conformity with those in the series of cases examined by us, from other sources, and quoted previously.

For the purpose of brevity we included under the term erythroblastosis all cases of moderate jaundice, anemia, icterus gravis, icterus hemolyticus, erythroblastosis, and hydrops fetalis. It may justly be asked as to where we draw the line between physiologic jaundice (icterus neonatorum) and the other forms just mentioned. The fact is that no one has yet drawn a distinct line of demarcation of the so-called physiologic jaundice and the advent of the pathologic state, save for the fact that icterus neonatorum is so termed because it disappears spontaneously. All forms of jaundice and anemias that occurred in our group of 3,791 cases are slightly over 1 per cent. It is hardly logical to apply the term "physiologic" to such a small percentage. It seems more likely that all jaundice in the newborn is pathologic; and that in all likelihood many of these will be explained by the discrepancy of the Rh factor in the mother and the father when routine Rh factor determinations are instituted in all pregnant women, and when erythroblastosis, especially in its mildest forms, is better recognized clinically. Javert¹⁰ gives an incidence of one case of erythroblastosis in 438 deliveries. Polayes gives an incidence of approximately one in a hundred cases.¹¹ Were we to consider only our fatal cases as the only true erythroblastosis, our incidence would approximate those of Javert.

A word about the treatment. We believe that many more infants would have died in this group had we not commenced treatment early and vigorously. As soon as a baby is born of an Rh-negative mother, a blood smear is made to determine the number of nucleated red blood cells. This is an immediate indication of the possibility of the baby developing erythroblastosis in some form. A count of over 10 should put one on guard. That baby needs a daily blood count for the next few days. A fall in the count, or anemia at the first count calls for immediate transfusion with Rh-negative blood. Transfusion is the anchor sheet. Too often is there too much tarrying and waiting and procrastinating before transfusions are resorted to. By that time there is too much hemolysis and too much liver and brain damage for the infant to overcome.

With this paper we have tried to show the great need for the routine determination of the Rh factor in all pregnant women. Indeed, may we even be bold enough to say that it should be made mandatory like the Wassermann test. We have purposely examined the hospital's records for positive Wassermann reaction, and we did not encounter a single positive case, nor a syphilitic baby in almost 5,000 consecutive admissions. Yet the Wassermann test was done in each of those cases. How much more important then, is the Rh factor determination in the light of the known facts concerning its importance for the mother should she require a transfusion, and for the baby should the mother prove to be of the Rh-negative type.

Summary and Conclusions

1. Discrepancy in the Rh factor is the most potent cause of intragroup transfusion reactions in Rh-negative women, particularly if they have recently been pregnant.

2. Our findings are similar to those quoted in the literature, that, with few exceptions, fetal erythroblastosis results from a mating of an Rh-negative female with an Rh-positive male.

3. New statistics and analyses are here presented which show that the male fetus is more susceptible to erythroblastosis fetalis than the female in the proportion of approximately 3:1, and in fatal cases approximately 5:1. The chances for a female recovering are, therefore, so much greater, thus offering one means of prognosticating the outcome.

4. We urge the adoption, by obstetric institutions, of the routine determination of the Rh factor in all pregnant women.

References

1. Landsteiner, K., and Wiener, A. S.: *Proc. Soc. Exp. Biol. & Med.* 43: 223, 1940.
2. Wiener, Alexander S.: *Blood Groups and Transfusion*, ed. 3, Springfield, Ill., 1943, Charles C Thomas, p. 250.
3. Levine, Philip: *Yearbook of Pathology and Immunology*, 1941, p. 508.
4. Levine, P., Katzin, E. M., and Burnham, L.: *J. A. M. A.* 116: 825, 1941; Burnham, L.: *AM. J. OBST. & GYNEC.* 42: 389, 1941.
5. Levine et al.: *AM. J. OBST. & GYNEC.* 42: 925, 1941.
6. Levine, Philip: *AM. J. OBST. & GYNEC.* 42: 165, 1941.
7. *Loc. cit.*,³ p. 368.
8. Polayes, Silik: Personal communication.
9. *Loc. cit.*,³ p. 250.
10. Javert, Carl T.: *AM. J. OBST. & GYNEC.* 43: 921, 1942.
11. Polayes, Silik: Personal communication.

✓ RUPTURE OF THE UTERUS*

J. HUFF MORRISON, M.D., ASST. SURG., P.H.S., AND LOUIS H. DOUGLASS, M.D.
(From the University of Maryland, School of Medicine)

IN 1941 Reese and Linn reported from this clinic on rupture of the pregnant uterus, the number of cases being 34. Since that report there have been seen 11 additional instances of this complication, and it is these 45 cases which form the basis of this report.

That the condition is one of general interest is evidenced by the recent literature upon the subject, in which many phases are considered, and a total of about 450 cases presented. In the tables which follow and in their discussion, these papers will be referred to from time to time and comparisons will be drawn.

The cases forming the basis of this report are from the clinics of the University Hospital, Baltimore, from 1920 through 1943, and from the Baltimore City Hospitals from its inception in 1935 to the same date. The incidence is 1:1,465 deliveries, which is quite close to the combined incidence above.

In this series there were 17 instances of rupture following previous section and we find that four of these had been low cervical operations, in every

*Read at a meeting of the Obstetrical and Gynecological Section, Baltimore City Medical Society, Jan. 12, 1945.

instance the original incision and the rupture being longitudinal. Since the longitudinal approach is more or less routine in our clinics, this is not surprising and should not be construed to mean that the transverse incision of the lower segment is safer. Indeed, should rupture occur in a subsequent pregnancy, the longitudinal tear might be preferred, since it shows less tendency to extend and involve large blood vessels, and lends itself the more readily to repair, a phase which will be considered later.

TABLE I. INCIDENCE

AUTHOR	TOTAL NUMBER OF DELIVERIES	NUMBER OF RUPTURES
Sheldon	47,554	26
Burkons*	17,793	12
Knowles	6,009	12
Dugger	318,103	105
Acken	25,935	15
Davis†	147,625	184
Sadowsky	9,079	13
Eastman	53,574	53
Present report	65,916	45
Totals	691,588	465

Total incidence 1:1,487 deliveries

*Burkons reported 45 cases of rupture but only gave the number of deliveries for 12 of these.

†Number of deliveries estimated.

TABLE II. CAUSE OF RUPTURE AND MORTALITY

	1920- 1929	1930- 1939	1940- 1943	TOTAL	MOTHER		BABY	
					REC.	DIED	BORN ALIVE	STILL- BORN
Pituitary	0	3	2	5	1	4	0	5
Previous section—classical	2	3	8	13	12	1	7	7*
Previous section—low	0	3	1	4	4	0	3	2*
Version and extraction	3	8	0	11	6	5	2	9
Accouchement forcé	0	0	1	1	1	0	0	1
Labor prolonged	0	0	1	1	0	1	0	1
Labor prolonged with breech	0	1	0	1	0	1	0	1
Labor prolonged with disproportion	0	0	1	1	1	0	0	1
Presentation transverse neglected	1	1	0	2	0	2	0	2
Trauma—abdominal, severe	0	0	1	1	0	1	0	1
Spontaneous	3	2	0	5	1	4	0	5
Total	9	21	15	45	26	19	12	35

*Twin pregnancy.

It would be interesting to report our incidence of rupture following the cesarean operation, but some of our patients go elsewhere for subsequent deliveries, others come to our clinics having had previous sections elsewhere, and, finally, our index does not list patients who have had previous sections. However, a recent survey shows that there have been done at the University Hospital alone, in the time covered by this report, a total of 1,088 cesarean sections with an uncorrected maternal mortality of 5.07 per cent. Of this number, 166 had one or more previous sections, but only 23 were operated on for this indication alone. From this it might be reasoned that if we were to adopt the policy of "once a cesarean always a cesarean," we would be almost certain to lose more than the one mother who died in this series.

This patient was a gravida ix, para viii, whose seventh pregnancy was terminated at the University Hospital in 1929 because of a central placenta previa. She should have been sterilized at this time but was not. Her eighth pregnancy was uneventful and delivery normal. The ninth pregnancy went to term and she entered the hospital in early labor. Pains were of poor quality and progress slow. After twelve hours she complained of symptoms which should have been recognized as danger signs but were not, and it was some

thirty-six hours later that the true condition was appreciated and the abdomen opened. The patient died on the fourth postoperative day, the main cause of death being infection. This, of course, was a definitely preventable death.

Implantation of the placenta under the section scar would appear to favor rupture and it is now a rule of both clinics to refer all patients who have had a section to x-ray for placental visualization. If the placenta is reported to be under the scar, the patient is delivered by an elective section.

Another most important factor in the individual who has had a previous section would appear to be multiparity. As pregnancies continue, the uterine musculature becomes definitely scarred and what was at one time a firm union becomes greatly weakened. Or if several (four or more) pregnancies have gone to term and a condition arises requiring section, the chances of an intact scar are greatly lessened. (This was illustrated by the case cited above). It would appear to be conservative obstetrics to sterilize these patients.

The eleven instances of rupture following internal podalic version and breech extraction are disturbingly eloquent of the danger of this operation. During the period covered by this report, version and extraction was done 431 times, the incidence of rupture being 1 in 39. If we were to exclude those cases in which the operation was done on the second of twins, the incidence would be correspondingly greater.

In the five cases in which pituitary extract was responsible for the rupture, it seems only fair to explain that none of these occurred in the hospital, all being referred from their homes after the accident.

The one case of rupture following trauma is interesting and deserves a short summary.

A young primigravida, about thirty-two weeks pregnant, was thrown a distance of some 20 feet from a moving automobile when it was in collision with another car and her abdomen struck a telephone pole with great force. When she arrived in the hospital she was in severe shock and died shortly thereafter. The diagnosis was ruptured abdominal viscus, probably spleen, and massive intra-abdominal hemorrhage. Time was insufficient for operation. Autopsy revealed a complete longitudinal rupture of the body of the uterus, about 24 cm. in extent, with the baby and placenta in the abdomen.

Those cases in which rupture occurred after prolonged labor followed the usual pattern and require no special comment. On the other hand, the case in which accouchement forcé was responsible is such a tragic example of bad obstetrics that a summary should be given.

A 36-year-old, white, para 8-0-0-6, went into labor at term at 5 p.m. She was seen by her physician two hours later at which time the pains were regular and five minutes apart. She was given two injections (pituitary?) after which the doctor introduced his hand into her vagina and told her he was "opening her womb." The injections had made her pains much harder, but suddenly they ceased and patient stated that she "felt funny." She was then sent to the hospital for "instrumental delivery." Condition was rather good upon admission and the head was at the level of the spines with no cervix felt. A simple midforceps was done and patient delivered of a stillborn baby. Bleeding followed delivery, and, exploring the uterus, a rent was found extending upward from the internal os into the fundus. Hysterectomy was done and the patient recovered.

To conserve time and to prevent useless repetition it would appear wise to insert several tables at this point and to discuss them briefly and collectively.

From a study of the tables several facts appear to be rather self-evident and need only a statement of fact: Complete ruptures are more often fatal than incomplete, both to the mother and child, ruptures occurring at home carry twice the risk of those occurring in the hospital where prompt treatment

TABLE III. SITE OF RUPTURE

Upper segment	15
Lower segment	20
Both	9
Not stated	1

TABLE IV. TYPE OF RUPTURE

		MOTHER		BABY	
		REC.	DIED	BORN ALIVE	STILLBORN
Complete	36	17	19	5	32
Incomplete	9	9	0	7	3

TABLE V. TIME OF RUPTURE

		MOTHER		BABY	
		REC.	DIED	BORN ALIVE	STILLBORN
During pregnancy	7	6	1	3	4
During labor	27	14	13	7	22
During delivery	11	6	5	2	9

TABLE VI. PLACE OF RUPTURE

		MOTHER		BABY	
		REC.	DIED	BORN ALIVE	STILLBORN
Ruptured at home	21	8	13	1	20
Ruptured in hospital	24	18	6	11	15

TABLE VII. PREOPERATIVE DIAGNOSIS

Rupture	23
Placenta, premature separation of (present in 2)	6
Disproportion cephalopelvic	2
Viscus, abdominal, rupture of	1
Placenta previa	1
Rupture of placenta, premature separation of	1
Not made	3
Not stated on history	8

TABLE VIII. TYPE OF DELIVERY

		MOTHER		BABY	
		REC.	DIED	BORN ALIVE	STILLBORN
Delivered from above	25	20	5	12	15
Delivered from below	17	6	11	0	17
Died undelivered	3	0	3	0	3

TABLE IX. TYPE OF TREATMENT

		RESULTS	
		RECOVERED	DIED
Uterus repaired	11	11	0
Uterus removed	25	15	10
Abdomen not opened	3	0	3
Undelivered	6	0	6

TABLE X. SITE OF PLACENTA IN SECTION RUPTURES

	UNDER SCAR	NOT UNDER SCAR	OUTSIDE UTERUS	NOT STATED
Classical	4	2	6	1
Low	1	2	1	0

TABLE XI. ELAPSED TIME FROM RUPTURE UNTIL OPERATION

		MOTHER		BABY	
		REC.	DIED	BORN ALIVE	STILLBORN
Immediate	6	5	1	3	3
1 to 5 hours	14	12	2	7	9
6 to 11 hours	5	3	2	1	4
12 to 23 hours	3	1	2	0	3
24 to 36 hours	3	1	2	0	3
More than 36 hours	1	1	0	0	1
Not stated	3	2	1	0	3
Undelivered	3	0	3	0	3
No operation	6	0	6	0	6
Operation for disproportion	1	1	0	1	0

TABLE XII. CAUSES OF MATERNAL DEATHS

Hemorrhage and shock	13
Infection	5
Uremia	1

TABLE XIII. PARITY

GRAVIDA	RUPTURES	RECOVERED	DIED
1	4	1	3
2	6	6	0
3	6	4	2
4	7	7	0
5	4	2	2
6	3	1	2
7	1	0	1
8	3	0	3
9	5	2	3
10	2	1	1
11	1	0	1
12	1	1	0
13	1	0	1
14	1	1	0

TABLE XIV. FETAL MORTALITY

		BORN ALIVE	STILLBORN
Ruptured at home	21	1	20
Ruptured in hospital	24	11	15
Delivered from above	25	12	15
Delivered from below	17	0	17
Undelivered	3	0	3
Operation within 6 hours	20	10	12
Operation more than 6 hours	12	1	11
Others	13	1	12
Ruptured during pregnancy	7	3	4
Ruptured during labor	27	7	22
Ruptured during delivery	11	2	9

TABLE XV. COMPARATIVE MATERNAL MORTALITY

AUTHOR	CASES NUMBER	NUMBER DIED	PER CENT
Sheldon	26	11	42.3
Burkons	45	17	37.7
Knowles	12	7	58.3
Dugger	105	65	61.9
Acken	15	7	46.6
Davis*	106	57	53.7
Sadowsky	13	6	46.1
Lynch	33	18	54.5
Potter	17	3	17.6
Eastman	53	25	47.1
Present report	45	19	42.2
Totals	470	235	50.0

*Maternal mortality given for only 106 cases.

can be instituted. In cases of rupture, delivery from below is not conducive to good results, except in unusual cases. Table II emphasizes the need for early diagnosis and the prompt institution of treatment, that is, laparotomy. In Table IX various types of treatment are compared, and at once one is struck with the excellent results obtained in those cases in which the uterus was repaired and allowed to remain in the abdomen. It should be added that these patients were all sterilized at the time of operation, since it was felt that these uteri should not again be subjected to the strain of pregnancy.

In Table XIII, the parity of the patients is considered and it can be seen that, although 23 of the 45 ruptures were in patients who had had from 0 to 3 previous pregnancies, only 5 of the 19 deaths were in this group.

While Table X is not conclusive, it is interesting, to say the least, to note the number of times the placenta was found under the site of rupture.

In Table VII it is seen that the correct diagnosis was made in only one-half of the cases prior to operation. Several facts may be responsible for this large percentage of errors: first, the condition is comparatively rare and is often not thought of, and second, these cases many times present a somewhat obscure picture. For example, in the cesarean section ruptures, the onset was frequently quiet and accompanied by a minimum of shock and vaginal bleeding. Abdominal tenderness and rather constant abdominal pain were usually present, but were at times not outstanding, and it was difficult to differentiate the cases from those of premature separation of the placenta.

Summary

Forty-five cases of rupture of the pregnant uterus are presented more or less statistically with a minimum number of conclusions and with no more comment than appears necessary to explain the tables.

References

- Acken, H. S., Jr.: *Am. J. Surg.* 49: 423, 1940.
 Alexander, J. M.: *Am. J. Surg.* 56: 379, 1942.
 Bill, A. H., Barney, W. R., and Melody, G. F.: *AM. J. OBST. & GYNEC.* 47: 712, 1944.
 Burkons, H. F.: *AM. J. OBST. & GYNEC.* 42: 75, 1941.
 Davis, H. B.: *Bull. Lying-In Hosp. N. Y.* 13: 125, 1925.
 DeLee, J. B.: *J. A. M. A.* 115: 1320, 1940.
 Dipple, A. L., and Brown, W. H.: *AM. J. OBST. & GYNEC.* 40: 986, 1940.
 Dugger, John H.: *Pennsylvania M. J.* 45: 437, 1942.
 Eastman, N. J., and Delf, Eleanor: *Subm. for Public Canad. Med. Jour.* 52: 376, 1943.
 Gordon, C. A., and Rosenthal, A. H.: *Surg., Gynec. & Obst.* 77: 26, 1943.
 Knowles, J. J.: *M. Rec.* 144: 125, 1936.
 Lynch, J. F.: *New England J. Med.* 221: 847, 1939.
 Murray, H. E.: *J. Obst. & Gynaec. Brit. Emp.* 35: 327, 1928.
 Phaneuf, L. E.: *Am. J. Surg.* 56: 379, 1942.
 Potter, Irving: *AM. J. OBST. & GYNEC.* 19: 289, 1930.
 Reese, J. M., and Linn, R. F.: *West Virginia M. J.* 37: 9, 1941.
 Rickards, C. E. B.: *Brit. M. J.* 1: 1359, 1938.
 Sadowsky, A.: *Am. J. Surg.* 55: 544, 1942.
 Sheldon, C. P.: *AM. J. OBST. & GYNEC.* 31: 455, 1936.
 Selsey, A. D.: *AM. J. OBST. & GYNEC.* 33: 857, 1937.

THE TREATMENT OF TRICHOMONAS VAGINITIS WITH A SULFONAMIDE COMPOUND

HELEN M. ANGELUCCI, M.D., F.A.C.S., PHILADELPHIA, PA.

(From the Department of Gynecology, Woman's Medical College of Pennsylvania, and the Woman's Hospital of Philadelphia)

THE voluminous literature which has of recent years accumulated on the subject of vaginal trichomoniasis has been authoritatively summed up by the report of the Council on Pharmacy and Chemistry of the American Medical Association in the Oct. 23, 1943, issue of the *Journal* of the Association.

Besides noting the inadequacy of much of the published data, the report emphasized the "difficulty of setting up satisfactory evaluation criteria with our present knowledge" of the subject.

The source of infection of *Trichomonas vaginalis* is still unknown—the pathogenicity of this organism is yet to be definitely proved. Thus all that can be said, after reviewing numerous publications, is that a vaginitis associated with *Trichomonas vaginalis* as a distinct clinical entity is practically universally accepted and, after consideration of the innumerable substances used in treatment, we can be even more definite in the statement that there is no specific therapeutic agent.

A scientific evaluation of methods of treatment is not to be hoped for without the use of control data, and this is practically impossible in the study of a condition which involves such wide margins of error as the cooperation of the patient, her general gynecologic and endocrine status, the possibility of repeated contaminations, the presence of associated bacterial infections, etc.

Trussell and Johnson¹ have carried out a very important series of studies of the effect on pure cultures of *Trichomonas vaginalis* in vitro of the various chemicals used in the treatment of this vaginitis. These reports are among the few truly scientific studies published on the subject. Important as they are, however, they can furnish only collateral data, for, as the authors themselves state, there are too many variable factors complicating the clinical picture. For instance, of three substances which were tested in a previous study by the writer,² namely, pieric acid, quinine sulfate, and sodium bicarbonate, and which gave practically uniform results, only one, pieric acid, was found to be trichomonacidal in these studies in vitro. Further, we note that the concentration of the therapeutic agent plays an important part in the results reported by Trussell and Johnson.¹ Sulfathiazole is reported as inactive as a trichomonacide in a 1:1,100 dilution, but as active in 20 per cent concentration in a jelly base of a particular pH.

The extreme variability shown in the reaction of different patients to the same treatment emphasizes the conviction that we are far from approaching a solution to this perplexing problem; and we have felt it necessary, therefore, to search for the method of therapy which, while giving at least as good results as any other method, does so with the least inconvenience and discomfort to the patient. We must admit that in choosing this particular compound, we were not uninfluenced by the magic word "sulfonamide," and that we were also prompted by curiosity as to what results would be obtained with a substance

that would undoubtedly have a powerful bacteriostatic action on the associated bacterial (mostly streptococcic) vaginal infection.

Method

In our previous study referred to above,² we had used three different types of treatment, which, while giving practically the same results, still involved some disadvantages, either because of difficulty in application or because of objection on the part of the patient on esthetic grounds. The medication we are discussing in this report appears to be free of these disadvantages. It consists of an ointment* containing 15 per cent sulfanilamide, 2 per cent allantoin, and 5 per cent lactose in a greaseless base, buffered to pH of 4.5 with lactic acid. It is expressed into the vagina by means of an applicator which delivers approximately 10 Gm. at each application, and is used twice daily by the patient, at bedtime and on arising. Blood sulfanilamide levels of less than 1 mg. per 100 c.c. of blood were found by Parks³ in 68 patients using this preparation by the same method. The ointment is odorless, nonstaining, nonirritating, and appears to spread over the vaginal and vulvar surfaces, and to be free of the particularly annoying property of discharging from the vagina and thus necessitating the use of tampons or vulval pads.

The ease and simplicity of its application assures the cooperation of the patient and, as far as local treatment is concerned, appears to fulfill the therapeutic objective set forth by the Council, of "thoroughness and persistence with the simplest and least messy procedure."

This clinical study was conducted during 1943 and 1944 at the Gynecological Clinic of the Woman's Medical College and of the Woman's Hospital, with the addition of a number of patients from private practice.

Material

One hundred patients, 62 white, 38 Negro, showing vaginal trichomoniasis were treated. The age incidence varied from 19 to 59 years, 72 per cent being between 20 and 40 years old.

Six of these patients were unmarried, 94 married, and of the latter, 32 were infertile.

The vaginal pH (nitrazene method) ranged from 5 to 7.5.

Subjectively, 94 per cent admitted having leucorrhea, 30 complained of vulvar and vaginal discomfort with pruritus and burning, one of pruritus only, six were not aware of any vaginal discharge.

Objectively, 98 showed leucorrhea of varying degree, two had no demonstrable leucorrhea, 56 had an acute vulvovaginitis, one with numerous condylomata acuminata. Twenty-two patients had cervicitis, 34 laceration and ectropion plus erosion of cervix, 28 had a coincident pelvic inflammatory disease, 8 had myomas, and one had a procidentia.

Patients were seen for periods varying from four to ninety-one weeks. The average period of observation was thirty-one weeks. The period of actual treatment varied from four to nineteen weeks, the average being eleven weeks.

Results

The same criteria were used as in our previous study.

We considered as good results: subsidence of symptoms, disappearance of trichomonads, and return of the vaginal mucous membrane to normal, this condition of normalcy being maintained throughout at least one menstrual cycle.

We classed as recurrences, cases where the vaginitis had definitely subsided, giving what we considered a good result, and suddenly recurred even if only to a minimal degree. Recurrences were invariably associated with the reappearance of the trichomonad in the vaginal discharge.

A cure was a period of six months without treatment, with freedom from symptoms and recurrences.

A failure was a case in which the trichomonads did not disappear during the course of treatment, four weeks being considered a reasonable period of trial.

*Allantomide Vaginal Cream (National Drug Co., Philadelphia, Pa.)

The following results were obtained:

Smears became negative after one week of treatment in 80 per cent of cases, after two weeks in 13 per cent of cases, after three weeks in 4 per cent, and after four weeks in 1 per cent of cases.

Good results in 98 per cent of all cases.

Failure in 2 per cent. (In one of these all inflammatory signs and symptoms disappeared in spite of the persistence of the trichomonal infestation.)

Recurrence if treatment was stopped in 16 per cent of cases.

Cases followed less than six months and showing no recurrences without treatment for at least four weeks: 14.

Cases followed more than six months: 52. Of these 8, or 15.3 per cent, were not cured, 44, or 84.6 per cent, were cured.

Summary

One hundred cases of *Trichomonas vaginalis* infestation in nonpregnant women were treated with a lactose-allantoin-sulfanilamide compound.

Good results were obtained in 98 per cent; permanent cures in 84.6 per cent.

The method was found therapeutically satisfactory and esthetically acceptable to the patient.

References

1. Trussell, R. E., and Johnson, G.: AM. J. OBST. & GYNEC. 48: 2, 1944.
2. Angelucci, Helen M.: AM. J. OBST. & GYNEC. 31: 1020, 1936.
3. Parks, J.: M. Ann. District of Columbia 12: 5, 1943.

THE TRANSMISSION OF PENICILLIN TO AMNIOTIC FLUID AND FETAL BLOOD IN THE HUMAN*

JOHN H. E. WOLTZ, M.D., AND HAROLD A. ZINTEL, M.D., PHILADELPHIA, PA.

(From the Department of Obstetrics and Gynecology and the Harrison Department of Surgical Research, School of Medicine, University of Pennsylvania)

THE occurrence of infection of the uterine contents in patients with prolonged labor and in those with premature rupture of the membranes may constitute an indication for chemotherapy. In these circumstances, it may be desirable to use penicillin if this drug is proved to be transferred to the amniotic fluid and to the fetus. Placental transmission to the fetus was demonstrated in a short series of patients by Greene and Hobby.¹ However, their studies did not reveal the presence of penicillin in the amniotic fluid. The present study was undertaken to determine the concentration of penicillin in the amniotic fluid and in the fetal blood after administration of the sodium salt of the drug to the mother by the intramuscular and intravenous routes, and to attempt to form a preliminary estimate of the quantitative relationships of these concentrations at various times after injection.

Method

Fifteen normal women in active labor were given sodium penicillin shortly before delivery. Eleven of these received 25,000 units of penicillin in 3 c.c. of physiologic saline solution intramuscularly. Three of the eleven patients did not deliver within three hours and,

*The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Pennsylvania.

TABLE I. CONCENTRATION OF PENICILLIN IN MATERNAL BLOOD, CORD BLOOD, AND AMNIOTIC FLUID FOLLOWING INTRAMUSCULAR INJECTION OF 25,000 UNITS EVERY THREE HOURS

	PATIENT	WEIGHT (KG.)	NO. OF IN- JECTIONS	MINUTES BETWEEN LAST DOSE AND DELIVERY	UNITS PER C.C. OF PENICILLIN		
					MATERNAL BLOOD	CORD BLOOD	AMNIOTIC FLUID
Group I (0-60 min.)	G. P.	69	1	13	0.312	0.039	0.039
	V. G.	49	1	14	0.312	0.000	0.000
	R. M.	83	2	46	0.078	0.000	0.000
Group II (60-90 min.)	D. D.	85	1	67	0.156	0.039	0.156
	L. M.	75	1	75	0.156	0.039	0.039
	J. D.	72	2	77	0.156	0.078	0.156
Group III (90-180 min.)	Y. D.	75	1	95	0.078	0.000	lost
	A. S.	66	1	106	0.078	0.000	0.000
	C. H.	72	2	138	0.078	0.039	0.039
	D. T.	85	1	146	0.000	0.000	0.000
	H. O.	59	1	175	0.078	0.039	lost

therefore, were given a second similar injection of penicillin at the end of the three-hour period. The results are given in Table I. In each case the interval between the administration of penicillin and the time of delivery given in Table I represents the time between the last injection of the drug and the time of delivery. Four patients received sodium penicillin in an aqueous solution of 5 per cent glucose by the continuous intravenous drip method at the rate of 10,000 units of penicillin per hour. The data for the second group of patients are given in Table II.

TABLE II. CONCENTRATION OF PENICILLIN IN MATERNAL BLOOD, CORD BLOOD, AND AMNIOTIC FLUID FOLLOWING CONTINUOUS INTRAVENOUS ADMINISTRATION OF 10,000 UNITS PER HOUR

PATIENT	WEIGHT (KG.)	TOTAL UNITS OF PENICILLIN	HOURS	UNITS PER C.C. OF PENICILLIN		
				MATERNAL BLOOD	CORD BLOOD	AMNIOTIC FLUID
E. S.*	78	200,000	20	0.156	0.156	0.156
O. J.	63	20,000	2	0.312	0.078	0.078
M. J.	65	20,000	2	0.078	0.039	0.078
H. T.	64	20,000	2	0.078	0.039	0.039

At the time of delivery, a sample of amniotic fluid was collected in a sterile container from the gush of this fluid which usually accompanies the end of the second stage of labor. After the umbilical cord was divided, a sample of cord blood was collected before the placenta separated from the uterus. During the third stage of labor or immediately thereafter, a sample of maternal blood was collected. All specimens were placed in sterile tubes which contained 65 "Toronto units" of heparin and immediately placed in an icebox. The determinations of penicillin concentration were made from four to twenty-four hours after the specimens were obtained. These concentrations were determined according to a modification² of the hemolysis method as described by Rammelkamp.³

For the purpose of interpretation, Table I has been arranged in three groups according to the interval between injection of penicillin and the delivery of the child:

- Group I — 0 to 60 minutes
 Group II — 60 to 90 minutes
 Group III — 90 to 180 minutes

In Group I (0 to 60 minutes after injection of penicillin), comparatively high maternal blood levels were reached while very little of the drug was found in the cord blood or amniotic fluid.

In Group II (60 to 90 minutes after injection of penicillin), the maternal blood levels were 0.156 units of penicillin per cubic centimeter. In each case there were significant amounts of penicillin in the cord blood and in the amniotic fluid.

In Group III (90 to 180 minutes after injection of penicillin), the maternal blood levels had fallen to 0.078 unit of penicillin per cubic centimeter or below, and penicillin was not found consistently in the cord blood and amniotic fluid.

*This patient's intravenous penicillin was discontinued forty minutes before delivery and blood was taken from the femoral vein of the newborn rather than the cord.

These data suggest that the maximum concentrations in the fetal circulation and amniotic fluid are found 60 to 90 minutes following intramuscular injection into the mother.

The intravenous administration of penicillin (Table II) had been continued in each case for a period of at least two hours before delivery, and in each case there was a significant amount of penicillin present in the cord blood and amniotic fluid. The one case in which the intravenous administration of penicillin had been continued for twenty hours, the maternal blood, infant blood, and amniotic fluid showed identical concentrations (0.156 unit per cubic centimeter). There was no evidence of penicillin toxicity to either mother or child in this case or in any of the other patients.

The fact that adequate penicillin levels can be produced in the amniotic fluid as well as in the maternal and fetal circulations suggests the use of penicillin in the treatment of certain types of intrauterine infection as well as its prophylactic use following premature rupture of the membranes and during prolonged labor. The dosage, mode of administration, and efficacy in these complications of pregnancy remain to be determined by future investigations.

Conclusion

Penicillin was found to be present in the amniotic fluid following the intramuscular and intravenous administration of the sodium salt of penicillin to the mother. The concentrations were comparable with those of the maternal and fetal circulations.

References

1. Greene, H. J., and Hobby, G. L.: *Proc. Soc. Exper. Biol. & Med.* 57: 282, 1944.
2. Beyer, K. H., Peters, L., Woodward, R., and Verve, W. F.: *J. Pharmacol. & Exper. Therap.* 82: 310, 1944.
3. Rammelkamp, C. H.: *Proc. Soc. Exper. Biol. & Med.* 51: 95, 1942.

THE EFFECT OF IRRADIATION ON THE FUNCTION OF THE OVARY IN YOUNG GIRLS

Supplementary Report

IRA I. KAPLAN, M.D., B.Sc., NEW YORK, N. Y.

(From the Radiation Therapy Department, Bellevue Hospital)

IN 1939¹ I reported the history of a case of a young girl who, at the age of 4½ years, received intensive irradiation, x-ray, and radium treatments for a pelvic tumor and who, in spite of this intensive irradiation, subsequently at the age of 12 years had normal menstruation. She continued to menstruate regularly until the age of 19 years. My reason for reporting this case at that time was to show that unwarranted apprehension was present in the minds of the clinicians regarding the effect of irradiation in girls and young women.

This present report is to bring this case to a final conclusion, albeit an unfortunate one.

On July 2, 1943, the patient reported to me, complaining of a painful area on the right side of the coccyx which made sitting down extremely uncomfortable. This condition had existed for about six months, continually growing worse, before she sought relief. On examination, I found a firm, regular, round nodule at the base of the spine to the outer border at the gluteal margin. The mass was extremely tender, not attached to the skin but not too firmly attached to the underlying tissues. It was not compressible. From July 2 until July 27 x-ray therapy was administered to the mass with apparent relief of symptoms. The patient was not seen again until Oct. 19, 1943. She had no complaints and there was no interruption of the normal menstruation. On Nov. 9, 1943, she again

reported increasing pain at the coccyx area on sitting down. Examination showed persistence of the tumor which was, however, still fairly movable. Surgery was advised and the tumor was removed on Nov. 11, 1943. Grossly, it consisted of a regular, round, semi-firm mass, encapsulated in a thin glistening fibrous cover. A cut surface showed a firm homogeneous grayish-white tissue.

Pathologically the neoplasm proved to be a neurogenic type tumor. Microscopic examination revealed a new growth composed of interlacing bundles of connective tissue and nerve fibers. In between were numerous, generally large, ganglion cells which occurred either singly or in groups. The tumor was a ganglial neuroma and apparently represented a metastasis of a malignant sympathicoblastoma.

The wound healed spontaneously and relief was given for a short time. Recurrent pains became very distressing and a course of x-ray treatment from Nov. 23, 1943, to Dec. 17, 1943, failed to give relief. X-ray therapy was again instituted in March, 1944. On April 7, 1944, she was again examined and a large tumor was felt through the rectum firmly filling the right pelvis. Surgical removal was advised. She was operated upon at the Roosevelt Hospital on April 24, 1944, but the tumor could not possibly be removed.

Microscopic examination was reported as follows: Sections from the central portion of the tumor reveal much degeneration and some necrosis. Peripheral areas of the sections reveal large cells with irregular cytoplasmic outlines. These cells have several nuclei, sometimes peripherally arranged. The nuclei are uniform in appearance, round, and frequently have a large nucleolus surrounded by a clear zone in the cytoplasm. The latter, stained with crystal violet reveals coarse granules of the Nissl body type. From the peripheries of these cells a number of fine fibrillary processes are given off. The intercellular material is made up of such fine fibrillary material. Other cells are oval and spindle-shaped, possessing bipolar fibrillary processes. In these areas no mitotic figures are seen.

A second type of structure is evident in other sections. The tumor reveals greater cellularity. The cells are oval and spindle-shaped. The fibrillary processes are less distinct. The nuclei are hyperchromatic. An occasional mitotic figure is seen. The cells are arranged in bundles of irregular size. A slight tendency to palisade arrangement of nuclei is present in some areas. Much necrosis is present in some of these areas. Blood vessels have well-formed walls.

This tumor is a ganglioglioneuroma that has undergone malignant neurinoma (neurogenic sarcoma, graded I).

The wound failed to heal, and on May 29, 1944, another piece of tissue was removed for examination and was reported as follows: Sections reveal ulceration and necrosis. Underlying structure is a neoplastic growth composed of spindle cells. Nuclei are large, rich in chromatin, oval in shape. Cytoplasm is granular, stained pink in color. Mitotic figures are present in moderate numbers; as many as 6 may be seen per high-power field. Cytoplasmic processes are short. Tumor is vascular. In some areas tumor cells are intimately associated with the capillary walls. In some areas there is palisade arrangement of nuclei. The diagnosis was spindle-cell sarcoma, neurogenic type, of buttock.

The patient persistently went downhill in spite of all measures taken, including x-ray therapy, and she died on Sept. 8, 1944. Autopsy in relation to the tumor was as follows:

The rectum is displaced anteriorly. Its wall is fixed to the capsule of the tumor by firm fibrous tissue. The mucosa is intact. On section, the muscularis and mucosal layer of the rectum are clearly visible and not involved. Bulging into the pelvis is a large, moderately firm, whitish lobulated tumor mass that measures about 15 cm. in greatest diameter. The capsule over it is smooth. The tumor mass is continuous with the large fungating mass partially necrotic that protrudes over the sacral area. The rectum and anal orifice are not involved. The skin is intact but it is displaced anteriorly. The tumor reaches to within 1½ cm. of the anal margin on the skin surface. The rectum is not distended. On multiple sections the tumor mass in some areas shows marked degeneration, pseudo-cyst formation, with lobules filled with clear fluid. In other areas the tissue is pale grayish-white in color; it is rather tough in consistency. The exposed portion of the tumor reveals large areas of dirty grayish necrosis and adjacent areas of hyperemia and hemorrhage.

Reference

1. Kaplan, Ira I.: AM. J. OBST. & GYN. 37: 158, 1939.

METASTATIC ADENOCARCINOMA OF THE CERVIX UTERI ASSOCIATED WITH PRIMARY GASTRIC CANCER

EDWIN L. WILLIAMS, M.D., NASHVILLE, TENN.

(From the Department of Obstetrics and Gynecology, Vanderbilt University School of Medicine)

ATTENTION was first directed to the relationship between malignant neoplasms of the gastrointestinal tract and secondary pelvic cancer in 1896 by Friedrich Krukenberg.¹ He described a tumor of the stomach associated with an ovarian neoplasm and designated the ovarian tumor "fibrosarcoma ovarii mucocellulare (carcinomatodes)." It is now well known that the "Krukenberg tumor" represents secondary carcinoma of the ovary associated with a primary colloid carcinoma of the gastrointestinal tract usually occurring in the stomach.

The primary location of the tumor has been variously described throughout the alimentary tract from the esophagus to the sigmoid.^{2, 3} The ovary, however, has uniformly been the seat of the secondary lesion. It is the purpose of this paper to describe a carcinoma of the cervix uteri occurring in association with a carcinoma of the cardiac portion of the stomach.

Case Summary

Mrs. M. J., a 32-year-old multipara, was admitted to Vanderbilt University Hospital, Aug. 28, 1944, with the chief complaint of persistent vomiting. Her present illness began ten months before admission and was initiated by nausea during meals followed by emesis of at least a portion of each meal. During the ten months prior to admission her weight decreased from 259 pounds to 134 pounds. She became extremely weak and was able to be out of bed only with difficulty.

She complained of pains in the lower abdomen which were never excruciating. Her menses had been regular in interval and flow but had increased somewhat in duration during the two or three months prior to admission to the hospital. She had recently noted mild dysmenorrhea. There was no history of severe menstrual pain. She had had no vaginal discharge. There was a history of mild intermittent constipation. Hematemesis and melena were absent.

General physical examination revealed evidence of recent weight loss but no other significant findings. Pelvic examination showed normal external genitalia. On bimanual palpation, the cervix, the fornices of the vagina, the anterior vaginal wall, and the parametria were found to be "woody" in consistency. The cervix was firmly fixed so that on manipulation all the surrounding structures moved with it. There was no evidence of ulceration or infection, but hemorrhage from the os was evident on inspection. The fundus of the uterus was normal in size, but was abnormally firm in consistency. There was no palpable enlargement of the tubes or ovaries. There was no intrinsic lesion of the rectum.

Esophagoscopy revealed a dilatation of the entire esophagus most marked in its lower third. Marked hyperemia of the entire esophageal wall was evident. An obstruction was found at the level of the diaphragm and there was apparently an infiltration of the wall in this area by a neoplastic process which had produced small areas of ulceration. A specimen was taken from this area for microscopic study.

Subsequently, the cervix was exposed and tissue was removed for examination. The cervix was indurated and bled freely when incised.

Cystoscopy revealed hyperemia of the bladder wall. The ureteral orifices appeared normal and ureteral catheters were easily passed.

Gastrointestinal roentgenography following a barium meal failed to demonstrate a lesion of the stomach or the small intestine.

Thirteen days after admission an exploratory laparotomy was performed. Examination of the stomach revealed a nodular mass high on the lesser curvature which extended into the esophageal hiatus. There were numerous small nodules scattered over the peritoneal surface

of the diaphragm. There was no apparent involvement of the liver. Nodules were scattered profusely over the surface of the peritoneum along the lateral pelvic walls, the surface of the ovaries, the omentum and the fundus of the uterus. The ovaries were not enlarged but were adherent to the posterior leaves of the broad ligaments.

Fig. 1.

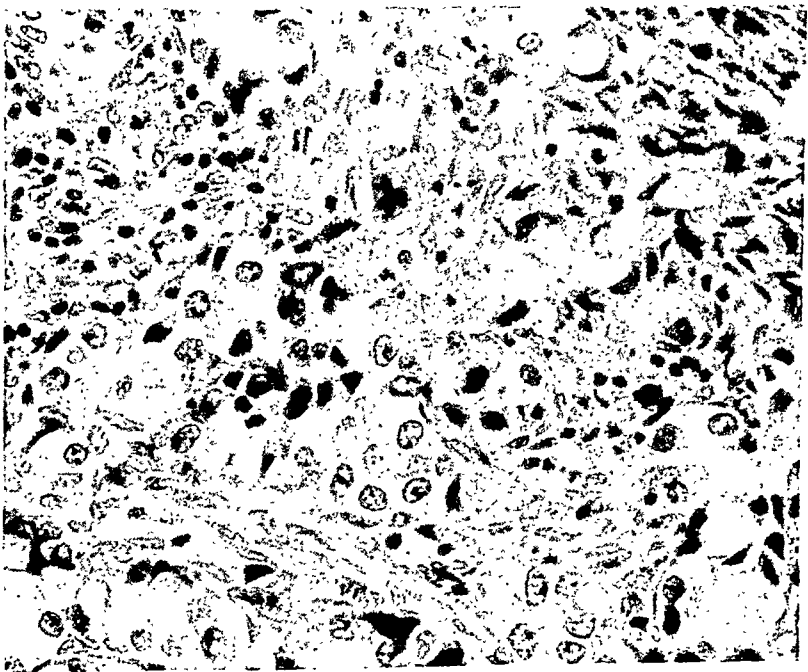
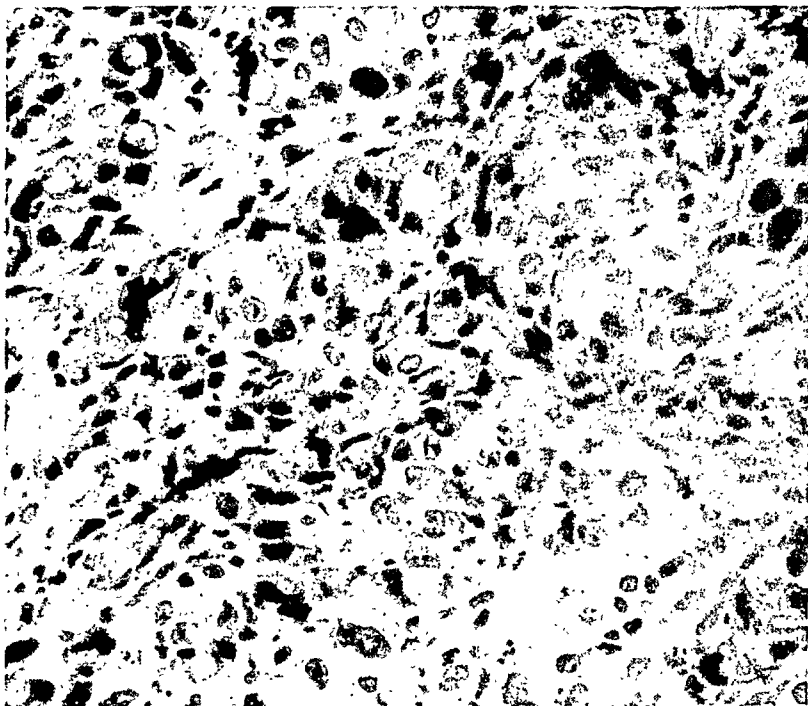


Fig. 2.

Fig. 1.—Primary adenocarcinoma of the stomach ($\times 500$).

Fig. 2.—Secondary adenocarcinoma of the cervix uteri ($\times 500$).

Biopsies were made from the lesion of the stomach, the omentum, and the peritoneal nodules. A gastrostomy was performed and the abdomen closed. The patient's postoperative course was uneventful.

Microscopic sections from the gastric lesion, the peritoneal metastases, and the cervix presented strikingly similar characteristics. The primary lesion consisted of anaplastic epithelial cells varying somewhat in size, shape, and arrangement and containing hyperchromatic nuclei. The nuclei in many of the cells were located eccentrically and were crowded

against the cell membrane, producing a "signet ring" appearance. An adenomatous arrangement of cells was present in some areas but was not uniform throughout. The stroma contained numerous small blood vessels. Sections from the peritoneal nodules and from the cervix were similar. The stroma of the cervical tumor was relatively more abundant and somewhat more dense but the epithelial characteristics were uniform throughout. The glandular arrangement of the cells and the mucoid content were remarkable.

The patient did not return to this Hospital inasmuch as she lived a great distance away.

Summary

1. Secondary adenocarcinoma of the cervix uteri may occur in association with a primary gastric cancer.
2. A case is presented which demonstrates this pathologic entity.

The author wishes to express appreciation to Dr. Lucius E. Burch, Obstetrician and Gynecologist-in-Chief, to the house staff, and to the members of the Departments of Surgery and Pathology who aided in the study and care of this patient.

References

1. Krukenberg, Friedrich: *Arch. f. Gynäk.* 50: 287, 1895-96.
2. Major, Ralph H.: *Surg., Gynec. & Obst.* 27: 195, 1918.
3. Chapman, T. L.: *Surg., Gynec. & Obst.* 31: 58, 1920.

TERATOMA OF THE PERINEUM IN A NEWBORN INFANT*

A. F. LASH, PH.D., M.D., CHICAGO, ILL.

(From the Department of Obstetrics and Gynecology and Pathology, Michael Reese Hospital and University of Illinois)

EMBRYONIC new growths of the perineum are rare. Thus under the heading "sacrocoecygeal tumors" in Abt's *System of Pediatrics*, Schultz states that mixed tumors arising at the caudal pole of the embryo are more numerous than those of the cranial pole. They may be situated within the pelvis, anterior to the sacrum and coecyx and behind the rectum; posterior to the bony structures and beneath the skin; or rarely, in the perineal region.

Schwalbe's classification of sacrocoecygeal tumors is as follows:

- I. A parasitic mass with more or less well-developed limbs or organs (pyopagus parasiticus).
- II. An external tumor is present, but organs or parts of organs are present only within the mass.
- III. Teratomas with derivatives of the three germ layers.
- IV. Mixed tumors with derivatives of only two germ layers, usually ectoderm and mesoderm.

Report of a Case

A female child, weighing 4 pounds, 12 ounces, was delivered in the thirty-sixth week of pregnancy, after six hours of labor, by prophylactic outlet forceps and episiotomy. The mother, a 35-year-old white gravida v, para o, gave a history of healed pulmonary tuberculosis, two induced abortions, one spontaneous abortion, and one twenty-week pregnancy terminated by abdominal hysterotomy because of placenta previa.

Examination of the infant revealed a normal development except for a red, glistening, smooth, cylindrical mass, about 2.5 cm. long and about 1 cm. in diameter, extending from the perineum just below the fourchette (Fig. 1). There was no communication with either

*Presented before The Chicago Gynecological Society, March 17, 1944.



Fig. 1.



Fig. 2.

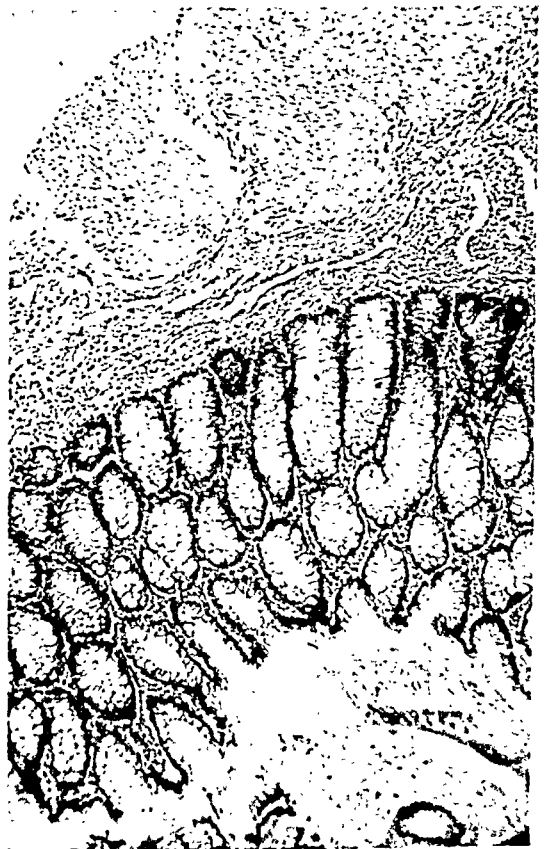


Fig. 3.

the vagina or the rectum. On the twelfth day after delivery, the mass was resected and the skin edges brought together. The wound opened on the sixth postoperative day but remained clean and closed by secondary intention. The baby has continued to thrive and develop normally.

Microscopic examination showed the external surface of the mass to be connective tissue with muscle fibers surrounding a cavity lined by glands resembling rectal mucosa (Figs. 2 and 3).

The teratoma in this instance was a mixed tumor consisting of derivatives from the entoderm and mesoderm and located in a rarely seen location, the perineum.

References

1. Abt, Isaac A.: A System of Pediatrics, Philadelphia, 1926, W. B. Saunders Co., Vol. III, p. 726.
2. Schwalbe, Ernst: Morphologie der Missbildungen, Jena, 1909, Gustav Fischer, Vol. III, p. 234.

30 NORTH MICHIGAN AVENUE

Department of Reviews and Abstracts

Selected Abstracts

Pregnancy, Complications, Etc.

Leon, J., Lascono, Gonzales, J. M., and Leon, C. T.: Hematomola of Breus. Diagnostic Difficulties Increased by the Biologic Reactions, *Rev. Asoc. méd. argent.* 57: 1108, 1943.

The authors report a case in a girl, 17 years of age, in whom the evolution of pregnancy seems to have been arrested between the sixth and eighth weeks, and retention in the uterine cavity was over seven months. The embryo had completely disappeared without even leaving traces of the umbilical cord. The most extraordinary observation was the positive result of three Friedman tests which increased the diagnostic difficulties. The authors emphasize the advisability of subjecting to critical judgment the results of the biologic tests. A positive result does not allow exclusion of a mole of Breus. Nor is it possible to fix within strict limits the hormonal rates which correspond to a normal pregnancy and to the various pathologic processes. In a case of discrepancy between clinical judgment and laboratory tests, the latter should be repeated, and the results of the clinical examination must principally be taken into account.

J. P. GREENHILL.

Bunster, Eduardo: Pregnancy at Term After Partial Hysterectomy, *Bol. Soc. chilena de obst. y ginec.* 8: 400, 1943.

The author had not found any such case in the literature at his disposal. The patient, 27 years of age, had been operated upon for a fibromyoma, 8.5 cm. in diameter, and the uterus had been reconstructed from its posterior wall and lateral borders. The author feared rupture of the organ during pregnancy and especially during labor. He calls attention to the capacity for regeneration of the uterus which, at the end of pregnancy, was nearly normal size and form. The organic adaptation was undoubtedly facilitated by the oligohydramnios which allowed maximal use of the available space for the fetal development. However, this space was slightly insufficient as shown by a slight facial asymmetry with which the child was born.

J. P. GREENHILL.

Varas, Osvaldo: Treatment of Nausea and Vomiting of Pregnancy With Vitamin B₆, *Bol. Soc. chilena de obst. y ginec.* 8: 404, 1943.

The author has used vitamin B₆ ampules of the Biochemical Laboratory Valparaíso, containing 5 mg. Injections were given intramuscularly every two to four days and their number varied from two to six, two being sufficient in most cases to obtain a definite result.

Seventeen patients were treated: all had nausea and vomiting and some were in serious condition. Twelve were immediately relieved by the first injection and all disturbances were stopped by the second. Relief in the other patients was also obtained, although more slowly. The action of the drug is so immediate and constant that, if it does not occur, it is well to suspect that some other disease is masquerading under the picture derived exclusively from the pregnancy.

In two cases, abortion occurred at least 15 days after the termination of treatment. The author does not think that there was any relation between the treatment and the abortion. One of the patients had previously had a spontaneous abortion.

J. P. GREENHILL.

MacLennan, Hector R.: A Case of Osteomalacia in Pregnancy, *J. Obst. & Gynaec. Brit. Emp.* 51: 127, 1944.

The author presents a case of acute osteomalacia complicating pregnancy. Blood studies are mentioned, as well as the dietary deficiency in this patient. Some facts, pro and con, are mentioned with reference to the comparison between rickets and osteomalacia.

WILLIAM BERMAN.

Russo, A. J.: Nausea and Vomiting of Pregnancy Treated With L-Histidine Monohydrochloride—Preliminary Report, *Virginia M. Monthly* 71: 522, 1944.

The use of l-histidine monohydrochloride in the treatment of peptic ulcer suggested its use in the treatment of hyperemesis gravidarum. Five patients with varying degrees of vomiting were treated by the intramuscular injection of 5 c.c. of l-histidine monohydrochloride. Complete relief was obtained in all. The author suggests that its beneficial effect may depend upon the power of the drug to relieve the hyperemia of the gastric mucosa.

WILLIAM BICKERS.

Kilkenny, G. S.: Diabetes in Pregnancy, *Wisconsin M. J.* 43: 622, 1944.

According to the author, the advent of insulin has complicated the management of the pregnant diabetic so that, although maternal and fetal morbidity and mortality have been lowered, the individual case still requires careful evaluation and attention. On the one hand, severe diabetes disturbs the metabolism of pregnancy, creating a hormonal imbalance leading either to abortion or to extremely obese babies prone to acidosis, the result of extremely high blood sugar levels. On the other hand, the pregnancy itself tends to produce acidosis in the mother, especially in the later months, with its attendant dangers. Careful attention to the size of the fetus at the eighth lunar month of pregnancy is advocated, and any evidence of excessive weight is indication for termination of the pregnancy.

The procedure for delivery is determined by the controllability of the diabetes and the energy-requirement factor of labor. In general it may be stated that a diabetic to be safely delivered by the vaginal route must have a blood sugar below 170 mg., no acidosis, and proper insulin balance. Cesarean section is strongly advocated as a prophylactic measure since it eliminates the energy-requirement factor and in this way allows for easier control of the diabetes.

FRANK SPIELMAN.

Lima, Octavio Rodrigues: Contribution to the Study of Vesicular Mole, *An. brasil. de ginec.* 18: 1, 1944.

The author describes the formation of the normal chorionic villi and the hormonal activity of the ovum, once it is fixed to the maternal organism, to facilitate the explanation of what occurs when vesicular mole develops. On the basis of the histologic study of his cases and of physiologic considerations, he supports the theory of vascular aplasia in the pathogenesis of vesicular mole rather than that of a degenerative process or chorionic neoplasm.

Histological examination of an expelled mole to evaluate its malignancy is superfluous because spontaneous expulsion alone is proof that at least these fragments are inactive. Examination of a surgically removed mole to deduce possible malignancy from its cytologic aspect is senseless because the curette or the finger removes only the part that was already prepared for elimination by cleavage. The cells retained in the depth of the uterine wall are those which will proliferate and present the characteristics of a neoplasm. Therefore, it is preferable to remove

the uterus which contains atypical and active chorionic elements, even though they do not yet have a clearly malignant character, rather than to preserve it in the vain hope that the trophoblastic activity will cease. It would seem that the intervention of a hormonal disequilibrium is necessary to cause the appearance of malignancy.

J. P. GREENHILL.

Smith, O. W., Smith, G. van S., and Hurwitz, D.: The Relationship Between Hormonal Abnormalities and Accidents of Late Pregnancy in Diabetic Women, *Am. J. M. Sc.* 208: 25, 1944.

Previously reported studies from the authors' laboratory have indicated that an abnormal rise in the chorionic gonadotropin (C.G., A.P.L., prolan) of the blood serum occurs in pre-eclampsia and eclampsia in both diabetic and nondiabetic women four to eight weeks prior to the appearance of any clinical signs. Although it is the most easily detected change, it is not as consistent a finding as urinary evidence of a changed metabolism of the placental steroids involving a progressive deficiency of estrogen and progesterin.

Hormonal studies in sixteen pregnant 'diabetic women were made, starting between the sixteenth and twenty-ninth weeks. Of these, only eight had normal offspring, and in fifteen some accident of late pregnancy occurred. Serum chorionic gonadotropin was repeatedly measured in all of the patients, and in eight the metabolism of the placental steroids was also investigated by repeated urinalysis for metabolites of estrogen. The results show that an abnormal rise in serum C.G. does not always precede the accidents of late pregnancy which so frequently are seen in diabetic women, especially those involving death of the fetus. Premature withdrawal of estrogen and progesterin, however, was a consistent finding in abnormal cases and an immediate precursor of either toxemia or death of the fetus. This change was preceded by such a marked increase in the production of the placental steroids that it could be recognized at least ten weeks prior to the clinical accident and five weeks before any rise in serum C.G. took place. To forestall the premature withdrawal of the placental steroids leading to the appearance of toxemia, a constant daily supply of estrogenic material may conceivably postpone the withdrawal until the maternal and fetal organisms are ready for delivery.

FRANK SPIELMAN.

Puerperium

Rotstein, Morris L.: Getting Patients Out of Bed Early in the Puerperium, *J. A. M. A.* 125: 838, 1944.

The author chose 150 patients at random who were delivered vaginally and allowed them up on the third and fourth day after delivery. Parity and type of delivery were not taken into consideration. No patient with any complication of pregnancy was included in this group. No ill effects were noted in this series. When allowed up, the patients felt well and were able to walk about and take care of themselves. They were allowed home from the sixth to the eighth day postpartum. A routine of postpartum care is outlined in the author's report. The patients are allowed up if the temperature for the preceding twenty-four hours is 99.6° F. or less. Involution of the uterus was accelerated and uterine prolapse was not encountered. The healing of episiotomies was not affected by this procedure. No cases of thrombophlebitis were noted.

WILLIAM BERMAN.

White, Robert A.: Puerperal Sepsis Treated With Penicillin, *South. M. J.* 37: 524, 1944.

A multipara, aged 25 years, went into spontaneous labor and promptly began to bleed from the vagina. Examination revealed a transverse presentation with shoulder presenting. Labor continued for fifteen hours, and at this time the cervix,

or that portion remaining, since a high amputation had been done previously, was three fingers dilated. A piece of placenta was palpable in the cervical os. Under ether, the cervix was dilated and a version accomplished. Profuse bleeding followed and the placenta was removed manually. The patient was in shock. Antishock therapy was instituted. The next day brought a temperature and chill following which the patient went into a typical puerperal sepsis which did not respond to transfusions, and a total dose of sulfadiazine, 25 Gm., over a period of several days, was administered without effect. When the patient appeared moribund, a supply of penicillin was obtained and given intravenously and intramuscularly. A total dose of 500,000 units over a period of forty-eight hours was given. Recovery was prompt and sustained.

WILLIAM BICKERS.

Radiation

Willan, R. J., and Shaw, Bernard, A. F.: A Case of Utero-Vesical Fistula After Radium, *Brit. J. Surg.* 31: 404, 1944.

The author reports a case of uterovesical (cervix) fistula which followed the use of radium in the treatment of metrorrhagia. The fistula was closed by a combined intraperitoneal and intravesical approach done in two stages. The patient made an uneventful recovery except to the extent that she lacked full bladder control when standing or walking when last seen by the doctor.

WILLIAM BERMAN.

Pohle, E. A.: Sterilization of the Ovaries by Roentgen Rays in the Treatment of Distant Metastases From Primary Carcinoma of the Breast, *Am. J. Surg.* 54: 490, 1941.

The effect of sterilization of the ovaries on metastatic carcinoma from a primary focus in the breast is discussed. Two cases demonstrating the efficacy of the treatment are reported. X-ray castration of all women regardless of age who have metastatic carcinoma from a primary carcinoma of the breast, as well as of all women 40 years of age or older who show no metastases following operation, is recommended. The author states that "the mechanism of the effect is not exactly known although there seems to be little doubt that the withdrawal of the hormones is responsible to a large extent."

FRANK SPIELMAN.

Molinari, Jose Luis: Roentgen Therapy in Ovarian Insufficiency, *Obst. y ginec. latino-am.* 1: 359, 1943.

Roentgen rays obey the general law of Arndt and Schultze, i.e., the same therapeutic agent acts as a stimulant in small doses, as an inhibitor in moderate doses, and with destructive effect in large doses. There is as yet no experimental proof that radiation produces excitation or stimulation directly, but indirect radio-stimulation is accepted by most authors and may be produced by various mechanisms.

The author presents an exhaustive review of the literature and summarizes the practical clinical considerations. According to Wolf, there are three principal causes of amenorrhea: (1) depressed function of the anterior pituitary lobe; (2) excessive quantity of stimulating estrogenic hormone, causing formation of single or multiple cysts without formation of corpus luteum; (3) excess of gonadotropic luteinizing hormone. In group 2, the endometrium is hyperplastic (polyhormonal amenorrhea of Zondek), and in group 3 it is in the premenstrual phase. Roentgen therapy over the pelvis will produce no results in group 1, but treatment of the pituitary is effective. In group 2, roentgen rays destroy the persistent follicles and yield good results. In group 3, destruction of the persistent corpus luteum causes menstruation in a premenstrual endometrium.

For irradiation of the ovaries, small doses of high voltage are employed. The technique usually recommended is 20 kv., 4 Ma., filter of 0.5 mm. copper, with addition of 1 mm. of aluminum, and a focal distance of 30 to 40 cm. The treatment

is administered to anterior and posterior pelvic fields, right and left, or a single pelvic field of greater size, anterior and posterior. When four fields are used the size is 8 by 10 or 10 by 15, and for two fields, 20 by 24 cm.

For irradiation of the pituitary, two lateral fields (6 by 8 cm.) are used. The dose is 75 to 150 r. (measured in air).

The first week, the pelvis is irradiated anteriorly; the second week on the posterior fields; and the third week again on the anterior fields. In rare instances, a fourth treatment is administered. Irradiation of the pituitary can be carried out at the same time as anterior irradiation of the pelvis.

Stimulating ovarian and hypophyseal irradiation produces favorable results in a high proportion of cases, many of which have been subjected to radiation treatment as a last resort. The dose administered for stimulation does not produce any unfavorable change in the mother or in children that might be born subsequently. Roentgen rays in stimulating doses administered with proper technique are a most effective agent in treatment of amenorrhea and sterility due to ovarian insufficiency.

J. P. GREENHILL.

Kenny, Meave: *The Clinically Suspect Pelvis and Its Radiographical Investigation in 1,000 Cases*, *J. Obst. and Gynaec. Brit. Emp.* 51: 277, 1944.

This report concerns the clinical roentgenologic correlation in 1,000 women which were classified as "suspect" problems for labor. The roentgenologic technique used was quite flexible, used to conserve on films. Dr. Kenny suggests the term "pithecoid" for the so-called "anthropoid" type, in order to convey, fitly, the sense "ape-like," and feels that a morphologic classification is essential in the analysis of the variable forms adult pelvis may display.

In over 80 per cent of the cases, the promontory was not reached and, as shown by radiographs, a false impression of pelvic adequacy at the brim might have been gained from clinical examination. The author also believes that vaginal examination in late pregnancy is more valuable for eliciting the shape of the lower fore-pelvis and lower sacral region, than for its popularly avowed purpose, the estimation of the diagonal conjugate. The short android hind pelvis plays an important role in dystocia. Although the author believes it is important to determine the intertuberous diameter and the width of the subpubic arch, it was interesting to note a small incidence of operative delivery when the lower fore-pelvis is narrowed and the hind pelvis adequate, as in the gynecoid-android type.

Prognosis regarding the probable outcome of labor, based upon the fetal pelvic relationship and pelvic conformation as revealed by roentgenograms, proved accurate and practical. This fact became helpful in an understanding of the principles of labor mechanism for standard pelvic types, useful in operative delivery and for teaching purposes. This point is particularly apparent from the successful use of Barton forceps in transverse arrest of the head in several instances.

From a small study series, a suggestion is offered that there may be a mother-daughter affinity in pelvic form. The author also concludes that a certain relationship between body build and pelvic shape exists. The android type was found to show a predisposition to develop toxemia of pregnancy, an observation also relating to the dystocia syndrome types of patient. It is of interest to note the incidence of rickets in Londoners (5 cases in 1,000), and osteomalacia (1 case), an incidence considerable lower (for rickets), than exists in this country.

During the six-year period devoted to the study, 10,000 women were delivered in the hospital and 94.8 per cent delivered spontaneously. The greater number of the operative deliveries from this large group occurred in the 1,000 cases selected for this report. However, the infant loss occurring in the operative group compared favorably with the low rate obtaining from all births in the unit.

The results of the study revealed the value of pelvic radiography in the diagnosis and treatment of obstetric difficulty due to malpositions or to pelvic abnormalities.

HOWARD C. MOLOY.

Contraception, Fertility, Etc.

Pommerenke, W T.: The Sterility Problem, West. J. Surg. 52: 295, 1944.

Requirements for pregnancy are: ovulation, spermatization, insemination, conjugation, migration, and nidation. The ovary must yield normal ova, normal spermatozoa must be produced and deposited near the cervical os, the uterotubal tract must permit union of egg and sperm and allow passage downward of the fertilized ovum, a healthy and prepared endometrium must await the fertilized ovum, and the nidation must persist for a period sufficiently long for the fetus to become viable. More frequent than those cases with some absolute sterility factor are those due to a summation of subthreshold defects.

About 12 per cent of all couples are involuntarily sterile and in these one will find a male defect in about 30 per cent. Study of the female should not be undertaken until the status of the male has been determined. Defects in spermatogenesis and obstruction of the vas are the most common male defects. Failure to produce normal ova and some mechanical obstruction in the uterotubal canal are the most common in the female. Immunization of the female by her husband's sperm with production of a spermatotoxin is suggested, and the early destruction of the ovum in a mother with anti-Rh agglutinins must be considered. A favorable environment for survival and motility of the sperm is provided by a glucose-saline douche just before coitus. Congenital hypoplasia of any part of the genital tract is a difficult sterility factor to combat. Study must include the Rubin test, basal metabolism, glucose tolerance, endometrial biopsy, and Huhner tests.

WILLIAM BICKERS.

Grafenberg, Ernest, and Dickinson, Robert L.: Conception Control by Plastic Cervix Cap, Western J. Surg. 52: 335, 1944.

A small plastic cap that adheres by a broad edge to the vaginal fornices is equal to the rubber diaphragm in its effectiveness as a contraceptive device. Clinical experience with this cervix cap has been extensive in Europe, and favorable reports from several well-known gynecologists are quoted. The cap may be inserted by the patient for a single coitus or may be left in place over a period of several weeks without discomfort or injury to the tissues. Follow-up on a large series of patients by these authors reveals only a slight redness about the fornices after the cap has been in place for several weeks and no permanent damage has been observed nor has any impediment to fertility upon discontinuance of its use been noted. It affords excellent protection against infection of the cervix from the vagina. Removal may be practiced after each coitus or it may be left in place and removed only during menstruation. The authors recommend a plastic cap available in three sizes which will meet all requirements. Especially is it indicated in those patients with cystocele or very short vaginal fornices where the diaphragm is unsatisfactory. It is also noted that some patients complain of discomfort with the diaphragm and occasionally the woman fails of the orgasm because the diaphragm covers the erogenous area just beneath the urethra. The properly placed cap cannot be displaced by the thrust of the penis.

WILLIAM BICKERS.

American Journal of Obstetrics and Gynecology

VOL. 50

OCTOBER, 1945

No. 4

Original Communications

ESTROGEN-PROGESTERONE THERAPY: A NEW APPROACH IN THE TREATMENT OF HABITUAL ABORTION*

Studies Indicating Its Rationale in 24 Treated Cases

NORRIS W. VAUX, M.D., AND A. E. RAKOFF, M.D., PHILADELPHIA, PA.

*(From the Department of Obstetrics, The Endocrine Laboratory and
Endocrine Clinic, Jefferson Medical College and Hospital)*

Introduction

MANY causes for habitual abortion and miscarriage are known or have been postulated. Among these are abnormalities of the ovum resulting from defects inherent in the germ plasm; maternal factors which influence pregnancy, such as inflammatory disease or tumors of the pelvic organs, febrile diseases, maternal syphilis, malnutrition, avitaminoses, incompatibility of blood types (particularly of the Rh factor), thyroid dysfunction and deficiencies of the hormones produced by the corpus luteum and the placenta during pregnancy; external factors, such as chemical poisoning, x-ray and radium, and trauma; abnormalities of the male germ plasm and constitutional diseases of the male. In the past the study of many such patients who have repeatedly aborted or miscarried has resulted in failure to find in a great majority of them any etiological factor which could be incriminated with certainty. This strengthened the belief commonly expressed that abnormalities inherent in the germ plasm constitute the largest cause for spontaneous abortion, particularly since it had been shown by a number of observers¹⁻⁴ that a high percentage of aborted embryos are pathologic. As pointed out by Meaker⁵ this concept has lost considerable support in view of the demonstration that many of these pregnancies can be saved and carried to term with the birth of normal babies, confirming the viewpoint of Mall¹ that these malformations may often result from external factors which have interfered with the growth, development, or nutrition of the embryo.

Much emphasis has been placed in recent years on the importance of endocrine factors in abortion; particularly those relating to functional failure of the corpus luteum and placenta. A sufficient number of studies are now available from a number of laboratories to indicate that abortion is sometimes preceded by

*Presented, by invitation, at a meeting of the Brooklyn Gynecological Society, March 2, 1945.

a marked fall in pregnandiol levels, pointing toward premature failure of the corpus luteum or inadequate function of the placenta.⁶⁻⁹ On the other hand there are also a number of reports that in some normal pregnancies low pregnandiol titers have been encountered while other patients may threaten to abort when pregnandiol titers are normal.^{6, 9} Finally, there are the therapeutic results with progesterone; like so many statistics on the treatment of abortion they are impossible of evaluation except to point out that they are conflicting.

In studies which we have made over a number of years on the blood and urine hormonal levels of normal and abnormal pregnancies, we have been impressed not only by the high percentage of habitual aborters who exhibit low pregnandiol titers but even more by the frequency with which these are associated with diminished blood and urine estrogen levels. Since both of these hormones are believed to be made by the corpus luteum during early pregnancy, these findings would support the diagnosis of premature failure of this structure; but since this same type of double deficiency was often noted by us after the first trimester, we were led to believe that the placenta can be equally responsible for the failure to produce estrogen and progesterone. These findings have encouraged us during the past three years to treat our habitual aborters with combined estrogen-progesterone therapy, despite early misgivings which we had concerning the administration of estrogens to patients who were threatening to abort or miscarry. During this time there appeared a report by Hamblen⁶ that progesterone alone failed to elevate low pregnandiol titers and to prevent abortion and that in a few cases the addition of estriol glycyuronidate did not help. More recently Hamblen⁷ states, "We believe that 'synergism' of progesterone with estrogen is advisable," and has employed it in the treatment of abortion.

Clinical and Laboratory Data

Patients.—The present study was made on a group of 24 women seen by us during the past three years in whom the previous two or more pregnancies terminated in abortion or miscarriage. These patients had gone through a total of 80 previous pregnancies (Table I) from which there had resulted only seven (9 per cent) full-term living infants, despite various types of treatment in many of the pregnancies. There were 52 abortions, 18 miscarriages, and one premature baby which lived only a few minutes. Twenty of these 24 women had no living babies. Eleven women were pregnant for the third time, 7 for the fourth time. In one patient seven previous pregnancies had resulted in abortion at the eighth to tenth weeks. One patient pregnant for the twelfth time had two living children, 5 abortions, and 4 miscarriages.

TABLE I. OBSTETRIC HISTORIES

Total number of patients	24
Total number of previous pregnancies	80
Abortions	52
Miscarriages	18
Stillbirths	2
Premature live births (did not survive)	1
Full-term live births (all normal)	7
Para 0 = 20	Grav iii = 11
Para i = 2	Grav. iv = 7
Para ii = 1	Grav. v or more = 6
Para iii = 1	

The ages of these patients ranged from 21 to 36 years. Fourteen women were less than 30 years of age.

A detailed analysis of the family and past medical histories of these patients did not reveal any factors which might be of etiological significance. There were no instances in which habitual abortion or miscarriage occurred in the mother or in sisters. No patients were included in this study who had pelvic tumors or other local abnormalities which might influence abortion, miscarriage, or premature labor.

Menstrual History and Fertility.—The menstrual histories of these patients were remarkably good (Table II) and compare favorably with those in similar groups of normal women. In 17, or 71 per cent, of the cases no marked deviation from normal was recorded. In 6 cases, episodes of hypermenorrhea, oligomenorrhea, or short periods of amenorrhea had occurred and one patient had a mild degree of menorrhagia.

From the standpoint of fertility (Table II) 13, or 54 per cent, of this group were able to become pregnant each time in less than six months and were classified as being of "good fertility."

TABLE II. MENSTRUAL HISTORY AND FERTILITY

	NO.	%
Normal menstrual history	17	71
Menstrual irregularity	6	25
Menorrhagia	1	4
Good fertility	13	54
Impaired fertility	2	8
Poor fertility	9	38

Two patients required from six months to a year to become pregnant and were classified as of "diminished fertility," while 9 patients were considered to be of poor fertility because they required more than a year for each conception; 4 of these patients had been under treatment as sterility problems. The percentage of patients with some impairment of fertility was probably somewhat higher in this group than average. There was, however, no correlation noted between degree of fertility and tendency to habitually abort. The patient with seven abortions had been married less than three years.

Studies Prior to the Present Pregnancy.—Fifteen of the 24 patients were seen before the present pregnancy began. In addition to careful physical examination, the following studies were made on these patients in as many instances as possible: Wassermann; Rh factor; basal metabolism; sounding of the uterine cavity, study of the endometrium obtained by endometrial biopsy or by dilatation and curettage; urine hormone assays including gonadotropins, estrogens, and pregnandiol. In the husband, the basal metabolism, Rh test, and a semen study were made. In the 9 patients who were already pregnant some of these studies had previously been made. Many of these tests, particularly the basal metabolism and hormone assays were repeated during pregnancy.

Wassermann: The Wassermann and Kahn reactions were negative in all 24 of these cases and were also found to be negative in all of the husbands. There was no history of antisyphilitic therapy in any of the patients.

TABLE III. STUDIES PRIOR TO PREGNANCY: BASAL METABOLIC RATE
(Average of two or more tests)

	NO.	PERCENTAGE
Patients tested	24	
Within + or - 15	23	96
Minus 20	1	4
Less than - 5	6	25

Basal metabolic rate (Table III): None of our patients exhibited frank clinical evidences of thyroid dysfunction such as thyrotoxicosis or myxedema. The prepregnancy basal metabolic rate in all our cases was within the commonly accepted range of + or -15 except one patient in whom the basal metabolic rate, made several times, averaged -20. She presented no distinct clinical features of hypothyroidism and had a normal serum cholesterol, but because of the hypometabolism she was regarded as "hypothyroid." Only six patients had an average basal metabolic rate less than -5.

Rh factor: A test for the Rh factor was made in all of the 24 cases (Table IV). In a majority of the cases the Rh had also been previously taken in this or other hospitals fol-

TABLE IV. STUDIES PRIOR TO PREGNANCY: RH FACTOR

	NO. OF CASES	PERCENTAGE
Rh test on mother	24	
Positive	22	92
Negative*	2	8
Rh test on father	14	
Positive	14	100
Negative	0	0

*Both husbands were Rh positive. Both patients were gravida iii (2 abortions each).

lowing the last abortion. Twenty-two of the patients were found to be Rh positive. Two patients were found to be Rh negative, and their husbands were Rh positive. Rh antibody titers were made at monthly intervals during the pregnancies of these two patients, but no agglutination occurred in a dilution of 1:1. One of these patients had a missed abortion, the other delivered a full-term normal baby. They had each had two previous abortions.

Examination of the endometrium (Table V): The endometrium was examined in eleven patients in the premenstrual phase.

The tissue was obtained by full curettage in two cases and by endometrial biopsy of at least two sites in nine patients. Urine hormone assays were made in the same cycle.

In two of the cases an interval endometrium was found, indicating that in these particular cycles ovulation had not occurred; estrogen and pregnandiol determination were also diminished in these instances. It is probable that in some of these patients with diminished fertility anovulatory cycles are frequent and in two other cases late proliferative changes were obtained with questionable or imperfect secretory function. In both of these cases estrogens and pregnandiol were diminished. In the other seven instances a normal secretory endometrium was obtained. In one instance a marked decidual reaction was noted and this patient was found to have been pregnant at the time the biopsy was taken; fortunately she carried to term.

TABLE V. STUDIES PRIOR TO PREGNANCY: EXAMINATION OF PREMENSTRUAL
ENDOMETRIUM
(Biopsy or dilatation and curettage)

	NO.	PERCENTAGE
NUMBER OF CASES	11	
Good secretory function	7	64
Impaired secretory function	2	18
Interval endometrium	2	18

TABLE VI. STUDIES PRIOR TO PREGNANCY: HORMONE ASSAYS

	NO.	PERCENTAGE
<i>Urine Gonadotropins</i>		
(Mid-cycle)	15	
Within normal	13	87
Diminished	1	7
Excessive	1	7
<i>Urine Estrogens*</i>		
(Mid-cycle & premenstrual)	15	
Within normal	5	33
Diminished	10	67
<i>Urine Pregnandiol*</i>		
(Premenstrual) (2 assays)	15	
Within normal	7	47
Diminished	8	53

*Eight (53%) of the 15 patients had a combined estrogen and pregnandiol deficiency.

Urine hormone assays prior to pregnancy (Table VI): Urine hormone assays were made in 15 cases. A 24-hour urine specimen collected at the mid-cycle was assayed for gonadotropins and estrogens. A 48-hour specimen collected one week later was assayed for estrogens and pregnandiol. The methods which we employ in our laboratory and the results obtained in normal cases have been published.¹¹

The gonadotropins were assayed by the mouse-uterine weight method on an alcohol precipitate of the urine. Estrogens were assayed on spayed mice on a carbon tetrachloride extract of the hydrolyzed urine. Pregnandiol was determined by the gravimetric method of Venning and Browne.¹²

Gonadotropins were found to be within normal (16 to 40 M.U.) in 13, or 87 per cent, of the 15 cases. In one case, in which there was also an interval type of endometrium, the gonadotropins were diminished; and in another associated with a normal secretory endometrium, a high value of more than 96 M.U. was obtained. We have occasionally noted such high values at the mid-cycle.

Urine estrogens were found to be within the normal range (32 to 100 M.U.) at both the mid-cycle and third week in only 5, or 33 per cent, of the 15 cases. Estrogens diminished below this value occurred in 10, or 67 per cent, of the cases; in 4 of these normal values

were noted at the mid-cycle but were low in the second specimen. In 9 of the 10 instances low values were noted during the third week; only one patient had a normal third-week value and diminished mid-cycle value.

Urine pregnandiol determinations were made in 15 cases. Values less than 2 mg. per 24 hours were considered diminished, and were encountered in 8 of the patients. In 3 cases no precipitate at all was recovered. In 4 of these 8 cases the endometrial findings were also abnormal. In 7 patients values of 4 to 12 mg. of pregnandiol per 24 hours were found.

Hormone Assays During Pregnancy.—Serum gonadotropins, serum estrogens, and urine pregnandiol were determined on 19 patients prior to the onset of treatment. In three instances these studies were repeated at monthly intervals during the course of treatment, while the other patients had at least one additional assay made during early pregnancy. The results given below are based on the initial assay made prior to the onset of treatment. It has been our routine to consider values less than 50 per cent of our average normal as diminished.

Serum gonadotropins: Serum was assayed for gonadotropic hormone in infantile mice by determining the least amount necessary to produce corpora hemorrhagica or corpora lutea in two-thirds of the mice and compared to the normal range previously published from our endocrine laboratory. In 18 cases, or 95 per cent, the values fell within the normal range. One patient showed diminished gonadotropins at six weeks, had an episode of spotting several weeks later, but went on to full term.

Free serum estrogen (Fig. 1): Free serum estrogens were determined in whole serum by studying the histologic response of the vagina of the castrate mouse to varying amounts of serum. Results were compared to normal values for the period of gestation as previously obtained in our laboratory. Diminished estrogen values were obtained in 15 of the 19 patients studied. In only 4 instances were the estrogen values considered to be within the normal range. The serum estrogen values made at approximately monthly intervals in three cases are shown in Fig. 1.

Urine pregnandiol (Fig. 2): Sodium pregnandiol glycuronide was determined by the gravimetric method of Venning and Browne¹² on complete 24-hour urine specimens in 18 cases. Fifteen of these patients showed pregnandiol levels which were diminished to 50 per cent or less of the normal expected value for the period of gestation. The repeat assays on 3 patients are also shown in Fig. 2.

TABLE VII. TREATMENT IN PREVIOUS PREGNANCIES

	NO.	PREGNANCIES SAVED
Patients treated	19	
Pregnancies treated	32	
Progesterone	21	0
Progesterone 20 mg. or more per week	11	
Estrogen and progesterone	1	0*
Thyroid extract	26	0
Vitamin E	20	0

*Successfully treated with estrogen and progesterone in next pregnancy.

Previous Treatment (Table VII).—Nineteen of the 24 patients received prophylactic treatment in the hope of preventing abortion during one or more of their previous pregnancies. In addition to increased amount of bed rest, therapy consisted of administration of thyroid extract, vitamin E, or injections of progesterone. Many of the treated patients received a combination of therapy. Treatment of this kind was administered in at least 32 of the 80 previous pregnancies. In 21 of the pregnancies it is known that progesterone was given bi-weekly by injection. In only 11 of the cases was the dosage known to be 20 mg. or more per week. None of the patients treated with progesterone in previous pregnancies carried to term. It is of interest that one patient who had had 11 previous pregnancies aborted during the third, fourth, fifth, and sixth pregnancies when she received progesterone but carried to term during the seventh pregnancy in which no treatment was given. In at least 26 of the pregnancies thyroid was administered and in at least 20 of the pregnancies vitamin E was taken.

One patient received progesterone, 10 mg. and estradiol, 10,000 rat units by injection twice a week during her last pregnancy and carried to the twenty-sixth week and miscarried. This patient delivered an almost full-term baby with similar treatment during this pregnancy when injections were continued to the thirty-second week.

Treatment During Present Pregnancy.—In this group of 24 patients treatment was limited to the injection of estrogen and progesterone except in one patient with a basal

metabolic rate of -20, who received 2 grains of thyroid extract daily in addition. Ten milligrams of progesterone and 10,000 rat units of alpha-estradiol benzoate* were given intramuscularly in the same syringe two to three times weekly. Treatment was started by the fourth week of gestation in six cases and by the tenth week in the remainder. Treatment was continued to term in eight cases. In six of these, patients fell into labor while they were still under treatment. One patient had treatment for three weeks only at which time she aborted. Wherever possible, treatment was continued at least to the twentieth week of gestation. The duration of treatment was adjusted as a rule to run beyond the time when the patient generally aborted or miscarried. Patients who had late miscarriages in previous pregnancies were generally given injection three times weekly as they approached the usual time for miscarriage.

No untoward local or general reactions to therapy were observed.

No vitamin E or other vitamin therapy was given except for the usual mixed vitamin capsule containing the minimal daily vitamin requirement which many of these patients were in the habit of taking. None of the patients were confined to bed except during episodes of bleeding, backache, or other symptoms suggestive of possible beginning miscarriage.

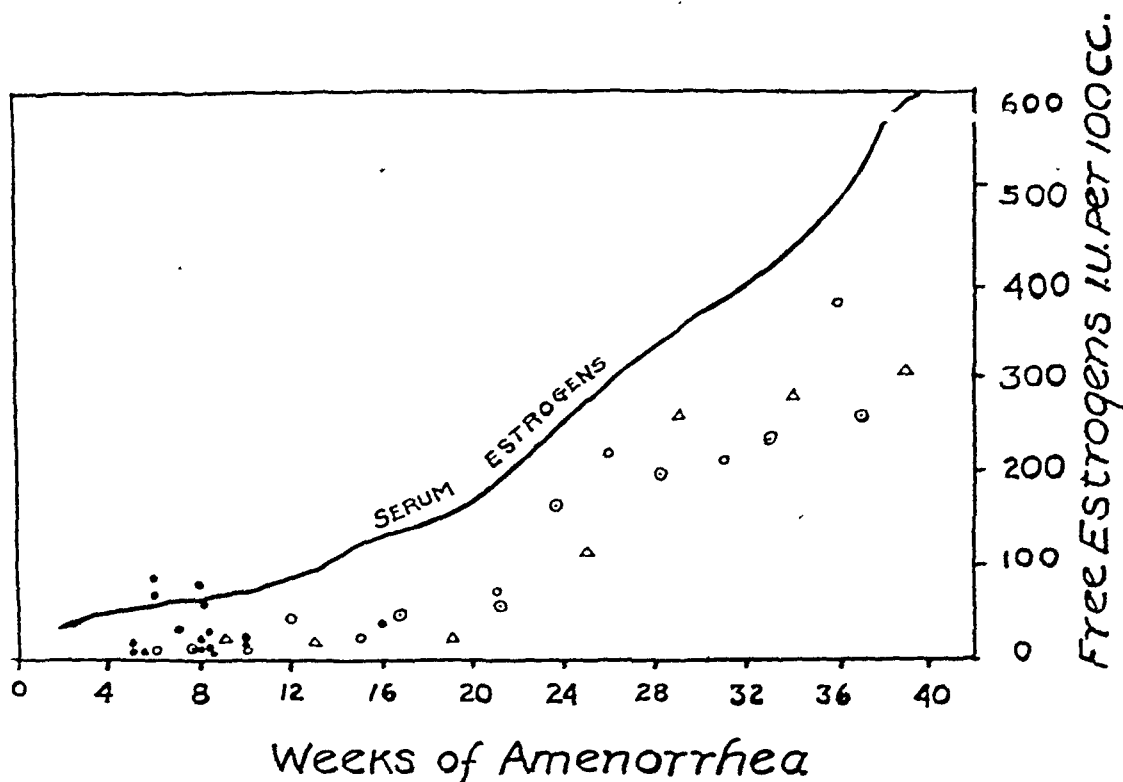


Fig. 1.—Curve showing the average normal serum estrogen values from data accumulated in our laboratory (by the method employed for these assays, 1 M.U. was equal to approximately 5 I.U. of estrone). The solid black dots indicate the serum estrogen values on initial assay in 19 cases studied.

○ indicates the serum estrogen values in A. K., gravida III, para 0, who was treated with progesterone and estrogen from the seventh week to the twenty-fourth week and delivered a full-term normal baby.

● The serum estrogen values in H. I., gravida III, para 0, who was treated with progesterone and estrogen from the eighth week to term and delivered a normal living baby.

△ Serum estrogen values on S. M., gravida IV, para 0, who was treated from the tenth week to term and delivered a normal living baby.

Results of Treatment (Table VIII)

Fifteen of the 24 patients had full-term live births. All of these patients had spontaneous deliveries without any unusual complications during labor. Of the 15 pregnancies, 14 of the infants were entirely normal and survived. One patient (A.R.) delivered a full-term living infant with multiple congenital abnormalities including an imperforate anus and polycystic kidneys, which died within twenty-four hours. This patient had two previous abortions and one early miscarriage. A number of Rh studies were made during her pregnancy because of conflicting results by different laboratories as to whether she was Rh positive or Rh negative. Blood was sent to Dr. Philip Levine who reported that she was Rh positive but of a rare subtype. Her husband was Rh positive. No antibody titer developed during pregnancy and the baby at term was not jaundiced or erythroblastic.

*Progesterone (Proluton) and alpha-estradiol benzoate (Progynon B) were generously supplied for many patients by the Schering Corporation.

TABLE VIII. RESULTS OF TREATMENT

	NO.	PERCENTAGE
Total Number of Pregnancies	24	
Full term live births	15	62
(1 Neonatal death due to congenital abnormalities)		
Premature live births	3	12
(2 survived)		
Miscarriages	2	8
Abortions	4	17
Total Number of Living Healthy Infants	16	67

Three patients delivered premature living babies at about seven lunar months' gestation. One of these weighed 4 pounds, was distinctly immature, and survived for only a few minutes. The other two premature babies survived and were otherwise normal.

Of the 4 patients who had normal serum estrogens and urine pregnandiol, 3 had normal living babies; the fourth was the patient referred to above (A.R.) whose baby died neonatally because of congenital abnormalities. Since these three patients did not have hormone assays made after the first trimester it is not known whether these patients developed estrogen and progesterone deficiencies later.

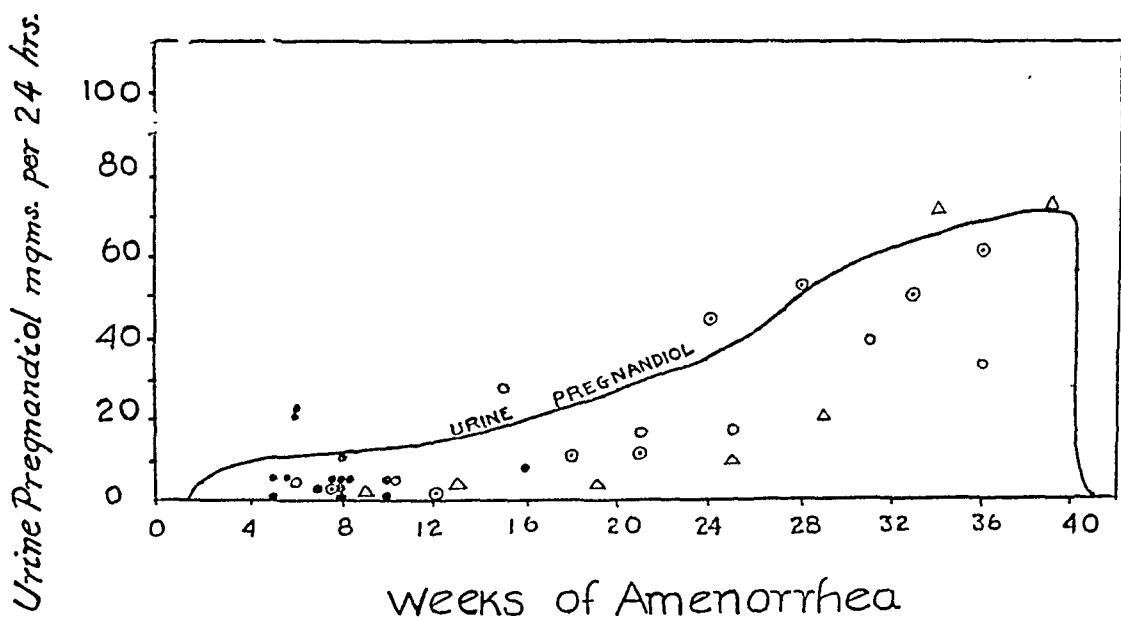


Fig. 2.—Urine pregnandiol values during early pregnancy on 18 patients before start of treatment. Pregnanndiol determinations throughout gestation are given for the same three patients indicated in Fig. 1. Curve shows average normal values from data accumulated in our laboratory.

Three patients who had low estrogen and progesterone values on their first assay during the early weeks of gestation, and who were treated with estrogen and progesterone, were followed at approximately monthly intervals by repeat hormone assays (Figs. 1 and 2). It will be noted that despite treatment the hormone values did not return to normal. During late pregnancy there was a tendency for occasional assays of estrogen and progesterone to be within the normal range.

Among the cases which were successfully treated during this pregnancy the following merited special description:

CASE 1.—C. K., aged 24 years. Past medical history and menstrual history entirely normal. Patient married in June, 1940, and became pregnant in October. Miscarried spontaneously in December. By February, 1943, she had had a total of seven spontaneous abortions at approximately eight weeks of gestation in each instance. During six of the pregnancies she received progesterone which in the last two pregnancies was given in a dosage of 20 mg. a week. She also received vitamin E in most of these pregnancies and in three of the pregnancies received thyroid extract despite the fact that the basal metabolic rate was always within normal. Physical examination was entirely negative. Wassermann was negative. The patient and her husband were both Rh positive. Semen analysis was normal. Endometrial biopsy made in the last week of the seventh cycle following her seventh abortion showed a secretory endometrium with a marked decidual reaction. Urine hormone assays made during this week showed pregnandiol, 2 mg. per 24 hours and diminished estrogens (22 M.U.

per 24 hours). When the menses failed to arrive at the expected date, a Friedman test was made one week later and found to be positive. Patient was immediately placed on progesterone, 10 mg. and estradiol, 10,000 rat units, three times weekly, which was continued until the twenty-sixth week and then reduced to twice weekly. The same treatment was continued except that after the twentieth week injections were increased to three times weekly and were continued to the thirty-second week of gestation. Two weeks later she delivered an apparently full-term normal living baby. Hormone assays made at the twentieth and twenty-eighth weeks of gestation showed normal pregnandiol and estrogen titers. Six months following delivery this patient again became pregnant and failed to return to her physician until spotting began at six weeks of gestation. She was again placed on progesterone and estrogen therapy three times weekly and at the present time is five and one-half months pregnant and has felt fetal life.

CASE 2.—M. N., aged 26 years, gravida iv, para 0. Physical examination negative except for moderate obesity. Menses were quite irregular recurring at four- to six-week intervals. Patient was of poor fertility and was treated with thyroid extract and gonadotropic hormone prior to the first pregnancy which terminated in a spontaneous abortion at ten weeks. She became pregnant again two years later after treatment with thyroid and progesterone and received injections of progesterone, 10 mg. weekly until the time of miscarriage at fourteen weeks. Two years later she again became pregnant. Several months before her third pregnancy she showed diminished estrogens and pregnandiol during the last half of the cycle. Her basal metabolic rate was -10. Patient and husband were both Rh positive. A semen analysis was normal. Hormone assays made at the sixth week of gestation showed diminished serum estrogens, diminished urine pregnandiol, and normal serum gonadotropins on two assays. She received injections of progesterone, 10 mg. and estradiol, 10,000 rat units, twice weekly until the twenty-fourth week when she delivered precipitately at home. The baby weighed 4 pounds but lived only for a few minutes. At autopsy it was found to be normal except for prematurity and immaturity. The placenta was grossly and histologically normal. This patient subsequently became pregnant again the following year. Hormone assays made at six weeks of gestation again showed low estrogen assays, made at the twelfth week of gestation continued to show diminished pregnandiol and estrogens but normal gonadotropins. Patient had an episode of bleeding at six and one-half lunar months which stopped in several days and patient was finally delivered at term of a mature normal baby. The placenta was found to be normal on histologic examination.

Unsuccessful Cases.—A total of six babies were lost during pregnancy by abortion or miscarriage; four in the first trimester, two in the second trimester.

CASE 1.—M. G. This patient had two previous abortions. She was first seen for this type of treatment at six weeks of gestation after bleeding had already started and received three injections a week for six weeks. Her basal metabolic rate was -6. Estrogen and progesterone values three months before pregnancy occurred were diminished. No hormone studies were made during pregnancy. She spotted throughout and finally miscarried at twelve weeks. During her second pregnancy she had received progesterone therapy 10 mg. twice a week until time of abortion.

CASE 2.—S. H. Had had one previous stillbirth, cause unknown, and two abortions. Studies made six months before pregnancy showed a normal secretory endometrium and normal estrogen and progesterone excretion during the last half of that cycle; however, hormone assays made at the fifth week of gestation showed normal serum gonadotropins with diminished estrogens and pregnandiol. This patient started treatment at the fifth week, received injections twice a week, and miscarried suddenly without preliminary symptoms at the fourth week. She also received thyroid extract, 1 grain, during this pregnancy.

CASE 3.—H. K., aged 29 years. Had had two previous abortions. She was Rh negative. Her husband was Rh positive. Hormone assays made two months before pregnancy showed normal estrogen and progesterone excretion, but assays repeated at the third week of gestation showed diminished estrogens and pregnandiol and normal gonadotropins. Treatment was started at the third week of gestation and she was given two injections weekly. After the tenth week the uterus failed to enlarge. At the twelfth week the pregnancy test was negative and the patient aborted the following week. No Rh antibody titer developed during this pregnancy. She had received progesterone in her previous pregnancies.

CASE 4.—E. P., aged 22 years, gravida iii. This patient had had two previous abortions. Basal metabolic rate before pregnancy was consistently low (average -20). No hormone studies were made before pregnancy. Assays made at the eighth week of gestation showed

diminished estrogens and pregnandiol and normal serum gonadotropins. Received thyroid extract, 2 grains daily. Injections of estrogen and progesterone started at the eighth week and were given twice weekly. The patient aborted four weeks later.

CASE 5.—E. R., aged 26 years, gravida iii. Had had two previous abortions. Had previously been treated with chorionic gonadotropin to correct menorrhagia believed to be due to a corpus luteum deficiency. Started treatment at the tenth week after bleeding had already started and aborted after three injections. She had been treated with progesterone and vitamin E in her last pregnancy.

CASE 6.—E. S., aged 34 years, gravida iv. First pregnancy resulted in a normal living baby and was then followed by two abortions. Her menstrual history was irregular and she was of poor fertility. Injections twice weekly started at the fourth week. The uterus failed to grow after the eighth week and the contents were expelled at four months. She had received progesterone and vitamin E in her last pregnancy.

There was a total of 18 live births of which 16 survived as living healthy infants making a fetal salvage average of 67 per cent.

Discussion

Endocrine Factors in Habitual Abortion and Miscarriage.—It is generally conceded that the corpus luteum in the human and in certain other species is essential for pregnancy by producing changes in the endometrium favorable to nidation, growth, and development of the fertilized ovum and by inhibiting uterine contractions during the period of implantation and the early weeks of gestation. This is accomplished largely through the action of the corpus luteum hormone, progesterone. It is important to recall, however, that the corpus luteum in addition to making progesterone makes considerable amounts of estrogens. These two hormones are intimately dependent upon each other in producing their physiologic effects. Estrogen is necessary to prime the uterus for the action of progesterone in producing a normal secretory endometrium. On the other hand, progesterone inhibits the excessive destruction of estrogens and facilitates the conversion of estrone to estriol.¹³ There is also reason to believe that unless estrogen and progesterone are present in the proper proportions inhibition of uterine contractions will not occur and that, as a matter of fact, a predominance of either hormone may destroy the delicate balance necessary to maintain uterine quiescence.¹⁴

It is known that in the human the corpus luteum is functionally active only during the early months of gestation. According to results following bilateral oophorectomy during pregnancy, the corpus luteum is generally essential for the normal continuation of gestation during the first trimester. Occasional pregnancies have persisted despite the removal of the ovaries even in the very early weeks of gestation.^{15, 16} The functions of the corpus luteum in making progesterone and estrogen are gradually taken over by the chorioplacental system.⁵ It is not known with certainty which cells make the estrogens and progesterone but it is believed on indirect evidence¹⁷ that both hormones are made in the syncytial cells of the placenta. During the early weeks of gestation the excretion of estrogen and progesterone in the urine rises but very slowly. It is not until about the eightieth day that the pregnandiol level rises distinctly above the level of 10 mg., its peak in the corpus luteum phase of the normal cycle. Estrogen excretion after this period is also considerably higher than at any time of the normal menstrual cycle. Throughout the remainder of pregnancy the estrogen and progesterone curves roughly parallel each other (Figs. 1 and 2). A few weeks before the onset of labor a large amount of estrogenic hormone which up to this time had been present almost entirely in the conjugated state now becomes freed,¹⁶ indicating important metabolic changes probably preparatory to

the onset of labor. There is also some evidence that shortly before the onset of labor there is a sudden drop in the pregnandiol level.¹⁹

In reviewing the hormonal physiology of normal pregnancy it is apparent that there are three phases in which deficiencies in estrogen and progesterone may develop: during (a) the immediate postovulatory phase when the corpus luteum may be inadequate because of insufficient pituitary gonadotropic stimulation or abnormalities resident in the ovary; (b) the phase of the corpus luteum of pregnancy, which may be inadequate either because of insufficient chorionic gonadotropic stimulation or local factors in the corpus luteum or ovary; (c) the placental phase, with inadequate production by the placenta after normal or premature failure of the corpus luteum of pregnancy.

Very little is known concerning failure of the corpus luteum immediately following conception. Studies of the endometrium showing poor or "immature" progestational response have been reported²⁰ but have been held open to question. In our present series there were two such instances of an "early" secretory endometrium. Moreover, more than half of the group of 15 patients studied prior to pregnancy had low urinary estrogens at the mid-cycle and during the third week, with diminished pregnandiol at the latter time. We are, of course, well aware of the dangers of attempting to draw conclusions from isolated hormone assays made on two occasions during one cycle; on the other hand, the findings are quite distinct from those commonly found by us in normal cases. If this syndrome of very early placental failure exists, undoubtedly there are many cases of very early abortion which go unrecognized.

The great majority of pregnancies are spontaneously lost during the first trimester when the bulk of the estrogen and progesterone is being produced by the corpus luteum of pregnancy. It is probable that the enormous amount of chorionic gonadotropin which is being produced at this time is largely responsible for maintaining the function of the corpus luteum. It would seem that deficiency of chorionic gonadotropin is not a frequent cause of corpus luteum failure since it was below the normal range in only one of 19 cases tested in our series. It is only when death of the fetus has been suspected that the chorionic gonadotropins begin to drop and do so quite precipitously. In our experience when the serum gonadotropins have fallen to less than 100 M.U. per 100 c.c. of serum, the fetus is usually nonviable.²¹ Administration of chorionic gonadotropin would therefore not be rational therapy as a rule; furthermore, the amounts required in terms of the quantity being produced in early pregnancy would be quite enormous.

The interpretation of diminished pregnandiol determinations in habitual aborters has been made difficult by the observation of diminished values in normal pregnancies.^{6, 9} We have also had the experience mentioned by others of a normal live birth following periods when very little or no pregnandiol was excreted on repeated examinations.

In our experience, serum estrogen values are much less subject to the marked day-to-day fluctuation which may be encountered in urinary estrogen values during pregnancy.^{22, 23} probably because the estrogens in the blood of pregnancy are largely present in a free state²⁴ and are not subject to the metabolic changes which occur in the kidney. In our experience a low serum estrogen value coupled with a low urine pregnandiol is of considerably more significance than the latter alone.

The rationale for the addition of estrogens to progesterone may be outlined as follows:

1. Progesterone and estrogen are believed to come from the same sources throughout gestation, and their concentration throughout gestation roughly parallel each other.

2. It is logical to assume that a deficiency in progesterone would be accompanied by a deficiency in estrogen.

3. In our experience such double deficiencies of estrogen and progesterone frequently occur in abortion patients, often appearing early in the gestation and persisting in many cases throughout the period of gestation.

4. There are good reasons to believe that estrogen and progesterone influence the normal reactions of each other upon the uterus and are involved in the normal metabolism of each other.

The early objections to the use of estrogen in abortion patients were chiefly on the basis that estrogens tend to increase the tonus and irritability of the uterus and to favor pelvic congestion. These statements can no longer be accepted as a generalization. Indeed the administration of estrogens in large dosages throughout a large part of pregnancy has been given with impunity to many patients for the treatment of diabetes complicating pregnancy.²⁵ On the other hand, estrogen in large dosage given to patients with missed abortion and intrauterine fetal death is known frequently to start uterine contractions. We have not been able to bring ourselves to believe that the use of estrogens alone in patients who are threatening to abort is physiologically sound or rationally indicated.

Endocrine Therapy.—There are many reports of a high percentage of successful results following the use of progesterone alone in the treatment of threatened or recurrent abortion. On the other hand, there have been an increasing number of studies in the past several years which have raised serious doubts as to the efficacy of progesterone as compared to similar groups which have not received endocrine therapy.²⁶⁻²⁸ Some clinicians have even expressed the opinion that in threatened abortion the administration of progesterone sometimes seems to precipitate expulsion of the products of gestation. Hamblen⁶ has suggested that progesterone administration may be undesirable because of possible inhibition of normal progesterone production and metabolism since he has noted that the excretion of pregnandiol was not increased, and occasionally even diminished, following progesterone therapy.

Our own results with progesterone alone, even in dosages of 40 mg. per week, have not been very encouraging. Many of our failures with progesterone therapy are represented in the previous pregnancies of some of the patients represented in this study. The poor results of progesterone therapy in this group cannot, of course, be considered representative of our general experience with progesterone since these cases were selected for further treatment because they were habitual aborters. There were, however, a number of patients in this group whom we had treated repeatedly in previous pregnancies with large dosages of progesterone without success in any instance.

If the administration of estrogen and progesterone in the dosage which we have employed constitutes complete replacement therapy, it might be expected that during the course of therapy the urine pregnandiol levels and serum estrogen would return to normal. Our observations on this point are rather disappointing. In three cases in which we have made observations at monthly intervals, normal levels did not occur until late in gestation when the effects of

administered hormone would have comparatively less influence on the high estrogen-progesterone levels. These observations raise the questions as to whether the dosage we employ is sufficient, whether the mode of administration is the best, and whether these patients may not have some abnormality of estrogen-progesterone metabolism. The last possibility deserves particular consideration in view of the fact that some of our patients exhibited low progesterone and estrogen levels in both the corpus luteum and placental phases.

Summary

1. A study was made of a group of 24 patients with habitual abortion who were treated with estrogen and progesterone.

2. These patients had gone through a total of 80 previous pregnancies from which there had resulted only 7 living babies (9 per cent). There had been 52 abortions, 18 miscarriages, 2 stillbirths, and one premature live birth in which the infant did not survive.

3. Fifty-four per cent of this group had no difficulty in becoming pregnant, 8 per cent were of diminished fertility, and 38 per cent were of poor fertility.

4. In none of these patients were there any pelvic abnormalities or systemic diseases which would influence abortion.

5. In only one patient was the basal metabolic rate diminished.

6. Two patients had Rh incompatibilities (Rh-negative wife and Rh-positive husband). One of these delivered a normal living baby and the others aborted; in neither case did Rh antibodies develop.

7. Examination of the endometrium obtained by biopsy or curettage was available in 11 cases before the present pregnancy. Good secretory function was noted in 7 cases, impaired secretory function in 2, and an interval endometrium in two.

8. Urine hormone assays were made in 15 cases prior to the onset of pregnancy. Urine gonadotropin assays made at the mid-cycle were normal in 87 per cent. Urine estrogens made at the mid-cycle and during the third week of the cycle were diminished in 67 per cent, while low or absent pregnandiol values were obtained in 53 per cent. Since these studies were made in only one cycle, their significance is limited.

9. Hormone assays consisting of urine pregnandiol determinations, serum estrogens, and serum gonadotropins were made early in pregnancy in 19 cases. In almost all of the cases one or more additional assays were made and in 3 cases monthly assays were done.

On the initial assay 95 per cent of the cases showed normal serum gonadotropins. Seventy-nine per cent had diminished serum estrogens and 83 per cent had diminished pregnandiol titers. In 13 of the 19 cases studied, both estrogen and pregnandiol were diminished. These findings indicate a deficiency of the corpus luteum during the early weeks of gestation and an inadequacy of the placenta to take over its functions.

10. Many of these patients had been unsuccessfully treated in previous pregnancies with progesterone, thyroid, and vitamin E.

11. During the present pregnancy all patients were treated by the injection of progesterone, 10 mg., and alpha-estradiol benzoate, 10,000 rat units, given together two or three times weekly. This treatment was generally continued to the period of viability or later.

12. There was fetal salvage of 16 babies, or 67 per cent. There were 15 full-term live births (with one neonatal death due to congenital abnormalities), 3 premature live births of which 2 survived, 2 miscarriages, and 4 abortions.

References

1. Mall, F. P.: *J. Morphol.* 19: 1, 1908.
2. Hertig, A. T., and Edmonds, H. W.: *Arch. Path.* 30: 260, 1940.
3. Rock, J.: Symposium on "The Abortion Problem." Auspices of the National Committee of Maternal Health, Baltimore, 1944, Williams & Wilkins Co.
4. Schultze, K. W.: *Ztschr. f. Geburtsh. u. Gynäk.* 121: 242, 1940.
5. Meaker, S. R.: *J. A. M. A.* 123: 680, 1943.
6. Hamblen, E. C.: *Endocrinology of Woman*, Springfield, Ill., 1945, Charles C Thomas, p. 476.
7. Hamblen, E. C., Cuyler, W. K., and Baptist, M.: *AM. J. OBST. & GYNEC.* 44: 442, 1942.
8. Browne, J. S. L., Henry, J. S., and Venning, Eleanor H.: *AM. J. OBST. & GYNEC.* 38: 927, 1939.
9. Hain, A. M.: *J. Endocrinol.* 3: 10, 1942.
10. Karnaky, K. J.: *South. M. J.* 35: 838, 1942.
11. Rakoff, A. E.: *M. Clin. North America* 26: 1915, 1942.
12. Venning, E. H., and Browne, J. S. L.: *Proc. Soc. Exper. Biol. & Med.* 34: 792, 1936.
13. Corner, G. W.: *Glandular Physiology and Therapy*, Chicago, 1942, American Medical Association, p. 189.
14. Hamblen, E. C.: *AM. J. OBST. & GYNEC.* 41: 664, 1941.
15. Pratt, J. P.: *Endocrinology* 11: 195, 1932.
16. Ask-Upmark, M. E.: *Acta obst. et gynec. Scandinav.* 5: 211, 1926.
17. Wislocki, G. B.: *Proceedings of the Conference on Problems of Human Fertility*, National Committee on Maternal Health, Menasha, Wis., 1943, George Banta Publishing Co., p. 134.
18. Cohen, S. L., Marrian, G. F., and Watson, M. C.: *Lancet* 1: 675, 1935.
19. Reynolds, S. R. M.: *Physiology of the Uterus*, New York, 1939, Paul B. Hoeber, Inc., p. 302.
20. Hamblen, E. C.: *Proceedings of the Conference on Sterility*, Auspices of the National Committee on Maternal Health, New York, January, 1945.
21. Rakoff, A. E.: *Pennsylvania M. J.* 43: 669, 1940.
22. Bachman, C.: *AM. J. OBST. & GYNEC.* 42: 599, 1941.
23. Smith, G. V., and Smith, O. W.: *AM. J. OBST. & GYNEC.* 39: 405, 1940.
24. Rakoff, A. E., Paschkis, K. E., and Cantarow, A.: *AM. J. OBST. & GYNEC.* 46: 856, 1943.
25. White, P., and Hunt, H.: *J. A. M. A.* 115: 2039, 1940.
26. Preliminary Report on Progesterone and the Status of Corpus Luteum Hormone Therapy, *J. A. M. A.* 116: 1523, 1941.
27. Paine, A. K.: *Bull. New England M. Center* 5: 33, 1943.
28. Bickers, W.: *AM. J. OBST. & GYNEC.* 43: 663, 1942.

807 SPRUCE STREET

Discussion

DR. SAMUEL A. WOLFE.—Dr. Vaux has proved chemically by hormonal assays the functional insufficiency of the corpus luteum of pregnancy as a cause of abortion. Yet for successful pregnancy that is only one of several factors. Additionally, a normally fertilized ovum, a normal embryo, as also a normal uterine decidua are essential. Systemic disturbances, such as the Rh factor, thyroid disorders, diabetes, etc., were of no great moment in the series presented.

We know little about the normal ovum or its fertilization. Whether fertilization by a deformed spermatozoon is a factor in eventual fetal malformation is only presumption. Certain it is that of all abortions occurring in the first month of pregnancy, only 25 per cent are normal. As pregnancy progresses, this incidence falls so that in the second month 50 per cent of embryos are normal. Certainly, a basically deformed embryo is not to be retained by any therapeutic agent. Molar disease of the trophoblast and early hydramnion are little understood. Fleshy moles and hematoma mole are further types of blighted ova which certainly cannot be affected by hormonal therapy.

The uterine endometrium, too, may not always prove a fertile field for implantation of the fertilized ovum. Mixed endometrial patterns occur and focal premenstrual changes (i.e., corpus luteum changes) have been seen in glandular cystic hyperplasia. Whether such uteri afford proper nidation and allow normal development of the fertilized ovum is entirely speculative. It would seem that hormone therapy could hardly help an organ which shows absence of normal response even in the nonpregnant state.

A normally functioning corpus luteum of pregnancy is a third requisite to maintain pregnancy in situ. Its deficiency has been proved by Dr. Vaux's work and the rational of the combined use of estrogen and progesterone rests on a sound basis. Since trophoblast is a normal pituitary stimulant this fetal element may indirectly be involved in the inadequate function of the corpus luteum. The combination of chemical studies in conjunction with examinations of the discharged products of conception would prove a more conclusive method by which to evaluate the effects of therapy. It must be noted that Falls attained excellent results in threatened abortions with a lutein extract free from progesterone. Karnaky using estrone by injection into the cervix also claims excellent therapeutic response to this agent. Shute and Miller-Vogt used vitamin E in threatened abortions, supposedly with excellent results. It would seem, therefore, that in many cases of abortion the results may be good not because of treatment but in spite of the therapy employed. Nevertheless, this paper has established the use of hormone therapy in habitual abortion not upon empiricism but upon a biologic basis.

DR. VAUX (closing).—The glycogen content of the endometrium has been referred to by Dr. Wolfe. That definitely has a very important part in this study. Complete studies of the endometrium and similar studies which we feel might lead us along a more trustworthy path have proved in our laboratory to be of great interest and very helpful in our investigation of habitual abortion.

There is a question as to what is an abnormal ovum. To begin with, we know that we cannot observe or control this finding. However, in the series of cases presented, we did everything possible in the laboratory and in this study to have very close association and coordination between the laboratory and the clinician. The Chief of our Endocrine Laboratory has been most helpful, doing most of the work, with regard to keeping the balance between the normal and the abnormal as far as the endocrinological side of this subject is concerned. We have felt that that was a very important part of the question of treating habitual abortion cases. We have found in many years of study, including laboratory investigations, that there was a great discrepancy in these two, the laboratory and the clinical side. When a balance was maintained we were at least 67 per cent better than previously when balance was ignored.

Corpus luteum failure is undoubtedly the basis of the deficiency in the progesterone and estrogen determinations. In pregnancy the levels were irregular and untrustworthy in a number of these patients when made previous to pregnancy and during the course of pregnancy.

The other important subject, I believe, is the cooperation of the patient. We were fortunate in having 24 of these women, who, as I pointed out, had 80 pregnancies and only 7 live births. They were treated very irregularly in their previous pregnancies and got tired of it and did not continue the treatment. We selected these women in the hope that we could throw a little further light on this rather interesting and very important topic of why so many of the patients we see in the clinic as well as in private practice habitually abort. We only hope we have added something of value and that future studies and discussions, as pointed out, may bring us to a very much happier conclusion.

RENAL GLOMERULAR AND TUBULAR FUNCTION IN RELATION TO THE HYPERURICEMIA OF PRE-ECLAMPSIA AND ECLAMPSIA

LEON C. CHESLEY, PH.D., AND LAURA O. WILLIAMS, M.D.
JERSEY CITY, N. J.

(From the Margaret Hague Maternity Hospital)

PERHAPS the most outstanding change in the blood chemistry in eclampsia and pre-eclampsia is in the uric acid, which usually increases. Stander and Cadden,¹ from a study of 148 cases, concluded that the blood uric acid "... gives us an accurate index of the severity of pre-eclampsia and the extent of liver damage, if present . . . and thus is our best criterion for any given type of treatment." As is implied in the quotation, these workers considered that hyperuricemia points to impairment of liver function.

The factors which, if uncompensated, would make for hyperuricemia are:

1. Increased production of uric acid in the body.
2. Decreased renal excretion.
3. Decreased destruction of uric acid in the body.

The question as to increased production of uric acid in pre-eclampsia remains unanswered, and almost unasked. As for the second factor, Cadden and Stander² reported normal excretion in five cases of eclampsia. By "normal excretion" they meant that the eclamptics, on a purine-free diet, excreted from 130 to 740 mg. of uric acid per twenty-four hours. This they compared with the 300 to 500 mg. excretion which Burian and Schur³ found in normal individuals. As we shall show in the discussion below, these data of Cadden and Stander may be reinterpreted.

Schaffer, Dill, and Cadden⁴ have measured simultaneously the clearances of diodrast, inulin, urea, and uric acid in normally pregnant and in pre-eclamptic women. They found that in pre-eclampsia the uric acid clearance averaged 31 per cent less than in their normals. They attributed the diminished uric acid clearance to a decrease in glomerular filtration (which showed a reduction of 20 per cent). Their data are open to the objection that they measured their clearances in the presence of plasma diodrast concentrations of the order of 1 to 2 mg. per 100 ml. Such plasma levels of diodrast will increase the uric acid clearance two- to threefold.^{5, 6} It is uncertain whether diodrast would have quantitatively the same effect upon the pre-eclamptic kidney as upon the normal. Furthermore, detailed study of their data for individual cases leaves one unconvinced that a reduction in the filtration rate is chiefly responsible for the decreased uric acid clearances. Recalculation of their data shows a more general factor—in pre-eclampsia there seems to be an increased tubular reabsorption of filtered uric acid. (Uric acid is filterable from human plasma.⁷)

In the present paper we are reporting the measurements of simultaneous clearances of inulin, urea, and of uric acid as determined by two methods. Inulin does not affect the uric acid clearance.⁵

Material and Methods

Antepartum clearances were measured in ten normally pregnant women near term. In eight of these, the clearances were repeated six to twelve days postpartum. Similar clearance determinations were made antepartum and repeated postpartum in eight cases of pre-eclampsia and two cases of eclampsia. No patient was in labor at the time of the test al-

though some delivered within twenty-four hours. (Crawford⁸ has found that the blood uric acid rises considerably during labor, perhaps because of retarded renal excretion.)

The night before the test, the patient was given a liter of water to drink. Beginning at 5:30 the morning of the test, she was given 200 ml. of water every half hour until the test was started (usually between 7 and 9 A.M.). The fasting patient was catheterized, a blank blood sample obtained, and an infusion set up. The infusion consisted of 700 ml. of 5 per cent dextrose containing 7 Gm. of inulin, and was given at the rate of 4 ml. per minute. Once the infusion was begun, 3 Gm. of inulin (in 10 per cent solution) were injected through the rubber tubing. At least half an hour later, the bladder was emptied, and a blood sample taken. Three urine samples were then obtained, usually at twenty-minute intervals unless the urine volume were low, in which case the collection periods were prolonged to as much as an hour. Further blood samples were taken midway in the second and again at the end of the third urine collection periods. At each emptying of the bladder, 50 c.c. of air repeatedly were blown into the bladder and suprapubic pressure used to force out the residual urine.

All clearances were calculated as $\frac{UV}{S}$, where UV is the quantity in milligrams of inulin, urea, or uric acid excreted per minute, and S is the concentration of the substance in the serum, in milligrams per milliliter. The data given in the tables are the averages of three clearance periods. Urine volumes were usually either decreasing or nearly constant.

Serum filtrates were made by the method of Somogyi⁹ for the inulin analyses. For urea and uric acid determinations, 3 ml. of serum were added to 13.5 ml. of distilled water; to this were added 1.5 ml. of 10 per cent sodium tungstate and, slowly with shaking, 12 ml. of N/12 sulfuric acid.

Inulin was determined in serum filtrates and in diluted urine by the fructose method of Roe,¹⁰ as suggested by Hubbard and Loomis.¹¹ Serum and urine analyses were done simultaneously and with a set of 5 standards (2.5 to 4.5 mg. per 100 ml.). This is important, because the color development is very sensitive to small changes in temperature, and the factor k, therefore varies. Readings were made with an Evelyn photoelectric colorimeter. Blood sugars were determined, since high concentrations of dextrose give some color in the inulin measurement.

Urea in serum filtrates and urine was determined by the manometric urease methods of Van Slyke.¹²

Uric acid in serum filtrates and in diluted urine was determined by (a) Folin's direct method,¹³ and (b) a modification of the photoelectric method described in the manual of the Rubicon Company.¹⁴ In this modification, the blanks were prepared by removing uric acid from serum filtrates and urines by treating with Lloyd's reagent. Folin¹³ writes that this treatment removes "all of the uric acid, nearly all of the creatinine, and very little else." The uric acid-free urines were then diluted to the same degree as were the samples for analysis.

All determinations, except urine urea, were done in duplicate.

Results

Tables I and II summarize the data for ten normal subjects. The individual clearances have not been corrected to the conventional surface area of 1.73 square meters. The averages, standard deviations, and ranges have been calculated from clearances so corrected. In estimating the surface area, the prepregnancy weights have been used. (Nearly, if not quite all studies of clearances in pregnancy have been corrected from the patients' actual weights, if corrected at all. Since the average patient near term weighs 20 to 30 pounds more than she did before pregnancy, or will weigh in a week or two after delivery, this makes an appreciable difference. We chose the prepregnancy weight because there is no evidence that the kidneys increase in size and functional capacity during pregnancy and recede rapidly in the puerperium. The usual correction for surface area is, of course, based upon the observation that renal size and clearances roughly parallel the body surface area. The uncorrected clearances are presented in the tables in order that the antepartum and postpartum values may be compared.)

There is no significant difference between the antepartum and postpartum averages. The average inulin and urea clearances of 128 and 78 ml. per minute, respectively, are about 10 per cent higher than the averages generally reported for women. The uric acid clearances as determined by the two methods check very closely, and are in the middle of the range reported for normal nonpregnant adults.

TABLE I. DATA FOR NORMAL PATIENTS, ANTE PARTUM
(Individual clearances not corrected for surface area)

NO.	AGE	GRAV- IDA	WEEKS PREG- NANT	SURFACE AREA IN SQ.M., FROM		SERUM URIC ACID, MG. PER 100 ML.	AVERAGE URINE VOLUME ML. PER MIN.	CLEARANCES IN ML. PER MIN.			
				PRE- PREG- NANT WEIGHT	ACTUAL WEIGHT DAY OF TEST			INULIN	UREA	URIC ACID	
										FOLIN	PHOTEL.
1	31	viii	42	1.57	1.81	4.87	7.84	129	81	13.4	14.0
2	20	ii	39	1.51	1.59	3.39	2.00	159	113	22.7	22.8
3	22	i	38	1.56	1.73	4.67	2.50	125	54	12.6	12.7
4	26	v	37	1.59	1.66	3.47	0.69	90	43	14.0	13.5
5	42	x	41	1.74	1.76	3.86	1.70	171	101	16.6	14.5
6	19	i	38	1.65	1.71	4.31	6.91	129	93	15.1	14.9
7	24	iv	40	1.63	1.71	3.92	4.14	127	53	16.8	16.8
8	33	vii	36	1.84	1.89	3.06	3.43	82	40	10.5	10.2
9	22	iii	35	1.64	1.68	3.21	2.76	143	101	17.0	15.9
10	23	iv	32	1.69	1.82	2.92	1.35	92	-	17.2	16.3
Averages				1.65	1.74	3.77	3.33	125	75	15.6	15.1
Clearances per 1.73					Averages			131	79	16.3	15.8
square meters body					Standard deviations			32	29	3.9	3.9
surface area, cor-					Ranges			77	38	9.9	9.6
rected from prepreg-								to	to	to	to
nancy weights								182	130	26.0	26.1

TABLE II. DATA FOR NORMAL PATIENTS, POST PARTUM
(Individual clearances are not corrected for surface area)

NO.	ANTE PARTUM				POST PARTUM							
	DAYS (A.P.)	URIC ACID/ INULIN CLEARANCE RATIO		DAYS (P.P.)	SERUM URIC ACID MG./100	AVERAGE URINE VOLUME ML./MIN.	CLEARANCES IN ML. PER MIN.				URIC ACID/ INULIN CLEARANCE RATIO	
		FOLIN	PHOTEL.				INULIN	UREA	URIC ACID		FOLIN	PHOTEL.
1	12	0.104	0.109	9	5.84	10.69	125	80	16.8	17.9	0.134	0.143
2	6	0.143	0.143	6	3.77	7.58	110	80	16.6	16.2	0.150	0.147
3	2	0.101	0.102	9	3.88	6.81	135	89	21.2	20.3	0.156	0.150
4	2	0.156	0.150	7	3.84	4.78	126	79	13.7	14.0	0.109	0.111
5	11	0.098	0.085	7	4.64	4.75	134	79	12.3	12.8	0.092	0.096
6	15	0.117	0.115	12	4.75	5.77	111	57	8.2	8.0	0.074	0.072
7	17	0.132	0.132	6	5.10	8.84	100	60	11.4	11.5	0.113	0.115
8	13	0.128	0.124	8	4.96	5.19	105	55	11.2	11.0	0.107	0.105
9	1	0.119	0.111									
10	22	0.187	0.177									
Averages		0.128	0.125	8	4.60	6.80	118	72	13.9	14.0	0.117	0.119
Clearances per 1.73		Averages					126	77	14.9	14.9		
square meters body		Standard deviations					16	16	4.7	4.6		
surface area, corrected		Ranges					99	52	8.6	8.4		
from prepregnancy							to	to	to	to		
weights							150	99	23.5	22.5		

Table III summarizes the rather meager literature on the normal uric acid clearance. Neither of the two papers dealing with uric acid clearances in pregnancy can be accepted as giving reliable values. Schaffer, Dill, and Cadden⁴ determined their clearances in the presence of diodrast; Nayar²¹ studied Indian women, whose average normals in many respects are far from anything seen in normal occidental women. Moreover, Nayar assumed that the rate of uric acid excretion has an augmentation limit at a urine volume of 2 ml. per minute, and arbitrarily used the square root of the volume in calculating his clearances. What he reports as "clearances" are therefore too low whenever the urine volume fell between 1 and 2 ml. per minute, since Bröchner-Mortensen¹⁹ found the augmentation limit to lie between 0.5 and 1 ml. per minute.

The clearance ratio of uric acid/inulin is of special interest. This ratio gives the proportion of filtered uric acid which is finally excreted in the urine. The lower the ratio, the greater has been the renal tubular reabsorption of filtered uric acid. In the ten normal cases, this ratio averages about 12.2 per cent (12.8 per cent ante partum and 11.7 per cent post partum). The lowest antepartum ratio is 9.8 per cent. There is no consistent direction of change with delivery; in 3 cases the ratio increased, in 5 it decreased, and in 2 no post-partum observations were made.

TABLE III. A REVIEW OF THE LITERATURE ON URIC ACID CLEARANCE IN NORMAL ADULTS ("Original formula" rephrased for uniformity. UV = minute excretion in milligrams. B, P, or S = blood, plasma, or serum concentration in milligrams per milliliter)

AUTHOR	YEAR	CASES	URIC ACID METHOD	URIC ACID CLEARANCE ML. PER MIN-UTE	CLEARANCE RATIO URIC ACID INULIN $\times 100$	ORIGINAL FORMULA
Watanabe ¹⁵	1917	5	Folin and Denis Benedict and Hitchcock	Whole blood 8.9	-	$\frac{B}{UV \times 60}$
Steinitz ¹⁶	1922	?	Hopkins- Morner	Whole blood 11.7	-	$\frac{B}{\sqrt{1.44 UV}}$
Berglund and Frisk ¹⁷	1935	76	Folin (1933)	Unlaked blood 19.0	-	$\frac{60 UV}{B}$
Gürdstam ¹⁸	1935	20	Folin (1922)	Plasma 13.5*	-	$\frac{UV}{P}$
Brøchner-Mortensen ¹⁹	1940	16	Own (Ferri- cyanide re- duction	Plasma 6.9	-	$\frac{UV}{P}$
Coombs and associ- ates ²⁰	1940	8	Benedict and Behre	Plasma 11.1	9.8	$\frac{UV}{P}$
Nayar ²¹	1940	43	?	Whole blood (7.7)†	-	$\frac{U \sqrt{V}}{B}$
Schaffer, Dill and Cadden ⁴	1943	12	Folin (1933)	Plasma (31.9)†	(30.3)†	$\frac{UV}{P}$
Bonsnes, Dill and Dana ⁶	1944	20	Folin (1922)	Plasma 14.6	-	$\frac{UV}{P}$
Present study	1945	10	Folin (1933) Photoelectric	Serum 15.7	12.2	$\frac{UV}{S}$
Totals and Mean		165‡		15.3		

*Averages of 8 to 9 and 9 to 10 a. m. periods. Bonsnes calculated an average of 12.9 for the first periods, Brøchner-Mortensen got an average of 11.9 for all periods.

†Not averaged. Nayar's formula does not give true clearances, and Schaffer and associates used diodrast.

‡Steinitz arbitrarily credited with ten cases.

TABLE IV. TOXEMIA PATIENTS, ANTE PARTUM
(Recorded observations refer to the day of the test)

NO.	AGE	GRAY- IDA	WEEKS PREG- NANT	SURFACE AREA IN SQ. M., FROM		BLOOD PRESSURE SYSTOLIC/ DIASTOLIC MM. HG	PROTEINURIA GRAMS PER LITER	EDEMA
				PREPREG- NANT WEIGHT	ACTUAL WEIGHT			
Pre-eclampsia								
11	23	vi	38	1.69	1.76	190/110	12	2 plus
12	26	i	41	1.49	1.59	158/102	12	3 plus
13	18	i	41	1.68	1.84	138/110	v. f. tr.*	2 plus
14	28	i	36	1.54	1.57	138/ 98	2	2 plus
15	43	v	41	1.89	1.87	142/ 92	v. f. tr.*	1 plus
16	31	iii	28	1.52	1.58	138/ 90	v. f. tr.*	1 plus
17	30	vi	30	1.73	1.89	160/100	10	3 plus
18	38	iii	34	1.58	1.67	160/114	34	3 plus
Eclampsia								
19	21	i	32	1.57	1.68	140/ 70	3	2 plus
20	18	i	38	1.59	1.82	160/110	30	3 plus

*v. f. tr. = very faint trace; slight turbidity on addition of sulfosalicylic acid.

Table IV describes the status of the pre-eclamptic and eclamptic patients, as of the day of the test. All had been hospitalized for some days before the tests were done; for this reason the recorded blood pressures, proteinuria, and degrees of edema often represent improvement over the status on admission. As for the 2 eclamptic patients, Case 19 was done

six days after a series of convulsions and intrauterine death of the fetus; Case 20 was done fifteen hours before the first of a dozen fits. All cases were known to have had normal blood pressures in pregnancy, until the onset of toxemia.

The antepartum clearance observations in the pre-eclamptic and eclamptic patients, which are summarized in Table V, show considerable reductions from the average normal. Thus, the inulin clearance averages 25 per cent below the average normal. Our average urea clearance is reduced in exactly the same degree, and thus the urea/inulin clearance ratio remains at the usual figure of 0.60. The uric acid clearance is decreased in considerably greater degree, and averages only 50 per cent of the normal mean. Cases 12 and 20 are not included in the averages, because the marked oliguria makes for probable collection errors. Of the eight cases with satisfactory urine outputs, only two had inulin clearances below the normal range (Cases 11 and 18). On the other hand, all but three did have uric acid clearances falling below the range of the normal series.

TABLE V. CLEARANCES IN PRE-ECLAMPSIA AND ECLAMPSIA, ANTE PARTUM
(Cases 12 and 20 not averaged because of oliguria)

NO.	SERUM URIC ACID, MG. PER 100 ML.	MEAN URINE VOLUME ML. PER MIN.	CLEARANCES IN ML. PER MIN.				URIC ACID/INU- LIN CLEARANCE RATIOS		DAYS BEFORE DE- LIVERY
			INULIN	UREA	URIC ACID				
					FOLIN	PHOTEL.			
			FOLIN	PHOTEL.			FOLIN	PHOTEL.	
Pre-eclampsia									
11	8.50	1.61	63	-	5.4	5.5	0.086	0.087	1
12	8.49	0.13	17	-	1.1	1.2	0.064	0.071	1
13	6.47	2.48	115	63	10.5	10.5	0.092	0.092	3
14	5.71	2.51	100	41	6.9	7.6	0.069	0.076	9
15	6.35	2.35	99	55	9.1	8.8	0.092	0.089	6
16	4.72	4.72	94	54	7.3	6.9	0.078	0.073	30
17	6.46	1.56	103	-	5.3	5.6	0.051	0.054	5
18	6.18	1.53	62	-	6.2	6.8	0.100	0.110	7
Eclampsia									
19	8.45	5.23	105	67	8.4	8.3	0.080	0.079	8
20	6.17	0.30	40	-	3.6	3.5	0.090	0.088	1
Means	6.61	2.75	93	56	7.4	7.5	0.081	0.081	8
Clearances per 1.73 square meters of body surface area, corrected from prepregnancy weight	Means		98	59	7.7	7.9			
	Standard deviations		20	10	1.7	1.7			
	Ranges		65 to 118	46 to 74	5.3 to 10.8	5.6 to 10.8			

TABLE VI. CLEARANCES IN PRE-ECLAMPSIA AND ECLAMPSIA, POST PARTUM

NO.	SERUM URIC ACID, MG. PER 100 ML.	MEAN URINE VOLUME ML. PER MIN.	CLEARANCES IN ML. PER MIN.				URIC ACID/ INULIN CLEAR- ANCE RATIOS		DAYS AFTER DE- LIVERY
			INULIN	UREA	URIC ACID		FOLIN	PHOTEL.	
11	6.29	7.55	103	63	8.3	8.2	0.080	0.079	9
12	4.32	5.75	148	93	19.8	21.4	0.134	0.145	6 months
	3.22	7.64	108	70	22.2	20.5	0.206	0.190	
13	4.84	5.40	100	66	13.0	14.2	0.130	0.142	8
14	4.21	5.58	80	-	11.3	13.4	0.142	0.168	7
15	5.88	3.95	113	78	10.7	10.2	0.095	0.090	6
	4.24	10.20	117	76	11.6	13.7	0.100	0.117	7 weeks
16	4.42	5.06	94	56	10.0	10.8	0.107	0.115	6
17	4.51	6.05	137	98	15.3	17.0	0.112	0.124	7
18	3.40	3.28	119	80	16.7	16.8	0.140	0.141	6
19	5.45	6.03	103	82	9.9	10.0	0.098	0.098	6
20	4.51	1.47	101	-	15.8	17.0	0.156	0.168	9
Means*	4.31	5.65	110	78	14.6	15.5	0.133	0.141	
Clearances per 1.73 square meters of body surface area, corrected from prepregnancy weight	Means	Means	117	82	15.6	16.4			
	Standard	Standard	18	12	3.6	4.4			
	deviation	deviation							
Ranges	Ranges	Ranges	90 to 151	64 to 98	9.8 to 25.8	9.3 to 23.8			

*In cases 11 and 15, only the second clearances are included in the averages.

The clearance ratio of uric acid/inulin is reduced by about one-third. With one exception, the highest ratio in the ten pre-eclamptics is lower than the lowest ratio in the ten normals (Fig. 1). This lowered clearance ratio points to an increased tubular reabsorption of uric acid in pre-eclampsia and eclampsia. This is the factor most generally operative in reducing the uric acid clearance.

The postpartum clearances in the pre-eclamptics and eclamptics show a return to normal (Table VI). Schaffer, Dill, and Cadden⁴ similarly found a rapid return to normal in the four pre-eclamptics whom they checked post partum, although part of the apparent increase is attributable to their corrections on the basis of weights at the time of the tests.

More significantly, the clearance ratio of uric acid/inulin also returns to normal after delivery. This ratio increased post partum in every case. As Fig. 1 shows, the ratio jumped from the low antepartum values up into the normal range in all but one case. In Cases 11 and 15, the ratios had not attained a normal level within the first week post partum. Repetition of the tests at six months and seven weeks, respectively, gave normal ratios.

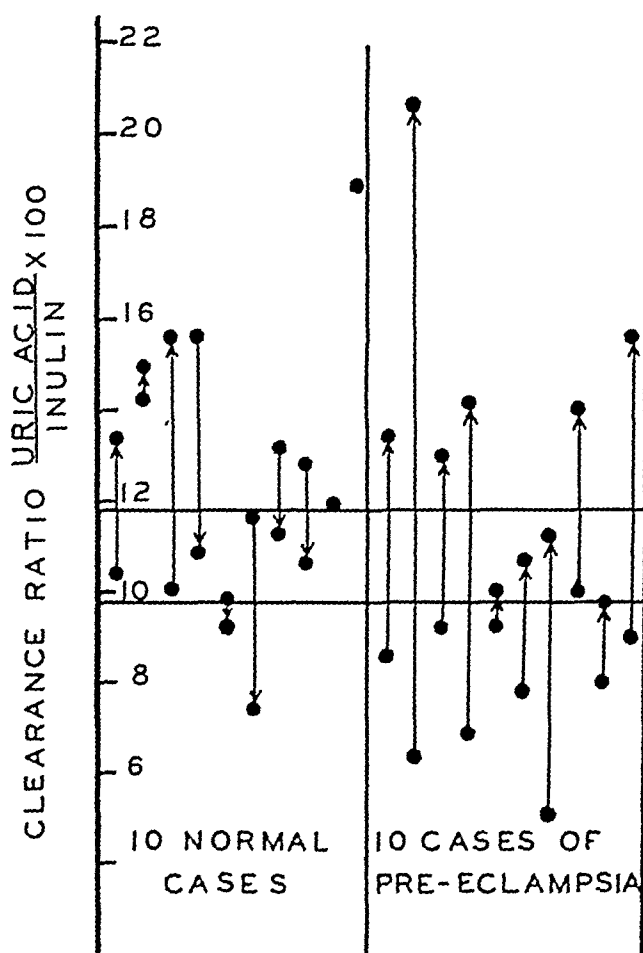


Fig. 1.—The fraction of filtered uric acid finally excreted in the urine. The arrow denotes the direction of change with delivery. (Clearance ratio = fraction excreted.) Upper line = average normal antepartum clearance ratio. Lower line = lowest normal antepartum clearance ratio. Note that the highest antepartum ratio in pre-eclampsia is lower than the lowest antepartum ratio in the normal series (one exception). Note also that every pre-eclamptic shows a rise in the ratio, with delivery, while there is no consistent direction of change in the normal series.

Discussion

Stander and Cadden,¹ in 1934, stated: "As yet we are not in a position to state that the excretion of uric acid is decreased in eclampsia. There is, however, sufficient evidence to make us believe that the accumulation of uric acid in the blood in eclampsia is not the result of decreased kidney function, but rather the result of a metabolic change. This metabolic change seems to be dependent upon liver damage." In 1939,² they concluded that the renal excretion of uric acid is normal in eclampsia (see above), and that the hyperuricemia therefore depended upon liver impairment.

The physiologic measure of the kidney's efficiency, however, is not merely the quantity of uric acid excreted in unit time. Rather, the true measure is the *clearance*. A clearance is calculated by dividing the quantity of substance excreted in unit time by the concentration of the same substance in the plasma. Thus a kidney of 50 per cent efficiency (clearance half of normal) will excrete the same quantity of uric acid in unit time as will the kidney of 100 per cent efficiency, provided that the plasma concentration of uric acid be doubled in the patient with the 50 per cent clearance. The five patients with eclampsia, studied by Cadden and Stander,² all had hyperuricemia. Dividing the "normal excretion" by the increased plasma concentrations would, then, give subnormal clearances. The rough calculations possible from their data indicate that all five of these patients had uric acid clearances of less than 50 per cent of average normal. A renal factor does, then, appear to be operative in the retention of uric acid in eclampsia.

As has already been mentioned, Schaffer, Dill, and Cadden⁴ found the uric acid clearance to be decreased by an average of 31 per cent in their pre-eclampsics. Our own data show an average reduction of 50 per cent in the uric acid clearance. The average serum uric acid in these toxemias was increased 75 per cent over the mean level in the normal series. The diminution in the clearance seems great enough to account for the rise in serum levels. If we assume a constant production and destruction (if any) of uric acid in these patients, then a 50 per cent reduction in the renal clearance might be expected to cause a rise, up to double the initial serum concentration. In several of our pre-eclamptic patients we predicted rises in the blood uric acid on finding low clearances. Thus, in Case 16, the whole blood uric acid was 3.5 mg. per 100 ml. on the day of the clearance test. The uric acid clearance was half of average normal. Two weeks later, the whole blood uric acid had climbed to 5.4 mg. per 100 milliliters.

From the above considerations, we see no need for invoking liver impairment as a causative factor in the hyperuricemia of pre-eclampsia and eclampsia. Our study has no immediate bearing upon the rest of the quotation from Stander and Cadden,¹ that the blood uric acid "... gives us an accurate index of the severity of pre-eclampsia. . . ." Whatever may have been established in this connection still stands; we question only that the hyperuricemia means liver damage. If an increased blood uric acid does point to severe pre-eclampsia, how are we to interpret a lowered uric acid clearance which will lead to a rise in the blood level? Is the clearance an earlier measure of severe toxemia?

In the averages, the diminution in the uric acid clearance is attributable to two factors exactly equal in effect. The factors are (a) reduction in the rate of glomerular filtration, and (b) increase in the tubular reabsorption of uric acid from the glomerular filtrate. But the uric acid clearance is often decreased while the filtration rate is normal. Therefore, the general factor in the reduction of the uric acid clearance in pre-eclampsia and eclampsia appears to be augmented reabsorption of uric acid by the renal tubules. This factor of increased tubular activity is expressed in the lowered clearance ratio of uric acid/inulin. As Fig. 1 shows, this ratio is decreased in every pre-eclamptic and eclamptic patient. Also, in every case, the ratio rises post partum while in normal patients there is no consistent direction of change with delivery.

The data of Schaffer, Dill, and Cadden⁴ include simultaneous antepartum clearances of inulin and uric acid in eight normal and seven pre-eclamptic pa-

tients. The clearance ratios calculated from their data are presented in Fig. 2. Their absolute values are not comparable to ours for the reason already mentioned (diodrast). However, it is clear that the clearance ratio is decreased in their pre-eclampsies where it averages 0.23; a reduction of 24 per cent from the mean ratio in their normals which is 0.30.

Whether the decreased uric acid clearance in toxemia represents renal "impairment" is a dialectic question. All evidence indicates that the reabsorption of filtered uric acid, in the normal subject, is an active tubular process rather than mere passive back-diffusion, as in the case of urea. In toxemia, this reabsorption is augmented. Since the clearance ratio of urea/inulin is normal, increased back-diffusion through damaged tubules probably is not operative. The kidney would, then, seem to be overactive in the reabsorption of uric acid, rather than underactive.

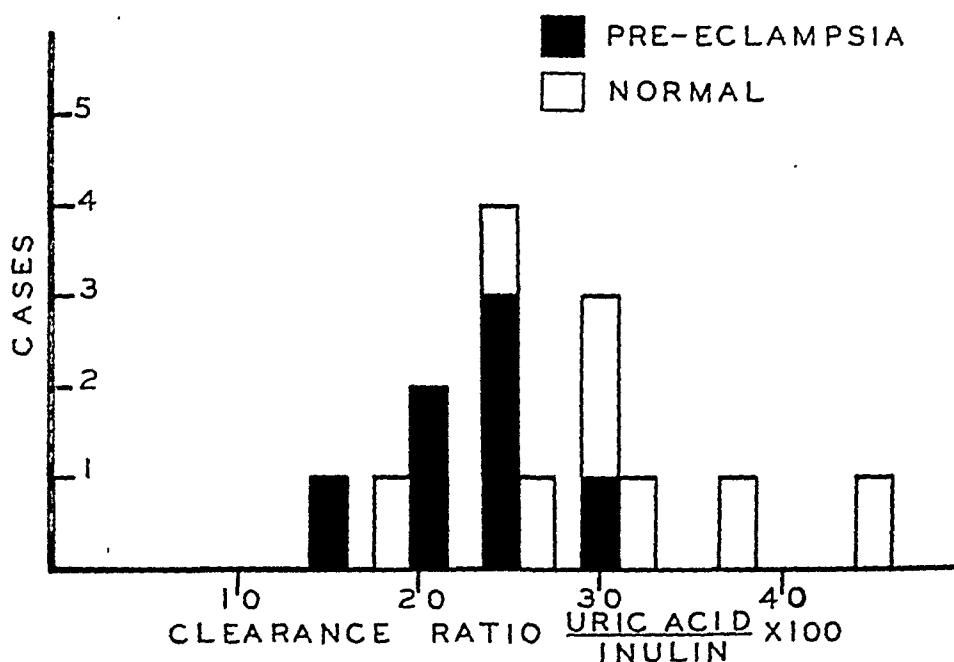


Fig. 2.—The $\frac{\text{uric acid}}{\text{inulin}}$ clearance ratios calculated from the data of Schaffer, Dill, and Cadden.⁴ The average ratio for the normal patients is 0.30, and for the pre-eclampsies is 0.23.

The effect of pre-eclampsia upon the uric acid clearance may be more marked than is apparent from the percentage depression in the clearance. Brøchner-Mortensen¹⁹ has shown that the uric acid clearance increases when the plasma level of uric acid is raised. Perhaps the spontaneous hyperuricemia of these toxemic patients also increases the clearances, and thus masks the true extent of the effect of the toxemia upon the renal tubule.

Our finding of a 25 per cent reduction in the urea clearance in pre-eclampsia is in accord with what other investigators have reported. At first sight it might seem to be in disagreement with an earlier paper by one of us,²² which has been criticized by Herrin²³ for reporting normal urea clearances in pre-eclampsia. In that paper, however, it is stated: "In all groups, the higher or highest clearance of several shown by a patient was taken as that individual's functional level if certain conditions were fulfilled." We do agree with the majority that many pre-eclampsies will show somewhat decreased urea clearances on single tests. Some will show persistently lowered clearances on repeated tests, but others will vary well up into the normal range in at least one of a series of tests.

Summary and Conclusions

Simultaneous measurements were made ante partum of the serum clearances of inulin, urea, and uric acid in ten normally pregnant patients near term, and in ten patients with pre-eclampsia and eclampsia. In all but two of the normals, the tests were repeated post partum.

In pre-eclampsia and eclampsia, the uric acid clearance is reduced. In this series, the diminution averaged 50 per cent.

On the average, the reduction in uric acid clearance depends equally upon 2 factors, viz.: (1) a decrease in the rate of glomerular filtration, and (2) an increase in the tubular reabsorption of uric acid from the glomerular filtrate.

The increased tubular reabsorption of uric acid is the more general of the two factors.

Published data of other workers have been reinterpreted to support these conclusions.

The diminution in uric acid clearance appears adequate to explain the hyperuricemia of pre-eclampsia and eclampsia.

We wish to acknowledge our indebtedness to Drs. S. A. Cosgrove, J. F. Norton, and E. G. Waters, who have permitted us to use their private patients, and who have read the typescript. The urea clearances and Duboseq colorimetry were done by Doris Furze and Eleanor Brudnicki.

References

1. Stander, H. J., and Cadden, J. F.: *AM. J. OBST. & GYNEC.* 28: 856, 1934.
2. Cadden, J. F., and Stander, H. J.: *IBID.* 37: 37, 1939.
3. Burian, R., and Schur, H.: *Arch. f. d. ges. Physiol.* 87: 239, 1910.
4. Schaffer, N. K., Dill, L. V., and Cadden, J. F.: *J. Clin. Investigation* 22: 201, 1943.
5. Talbott, J. H.: *Gout. Oxford Medicine*, Vol. 4, part 1, Chapt. IV, New York, 1943, Oxford University Press.
6. Bonsnes, R. W., Dill, L. V., and Dana, E. S.: *J. Clin. Investigation* 23: 776, 1944.
7. Smith, H. W.: *The Physiology of the Kidney*, New York, 1937, Oxford University Press, p. 195.
8. Crawford, M. D.: *J. Obst. & Gynaec. Brit. Emp.* 46: 540, 1939.
9. Somogyi, M.: *J. Biol. Chem.* 86: 655, 1930.
10. Roe, J. H.: *IBID.* 107: 15, 1934.
11. Hubbard, R. S., and Loomis, T. A.: *IBID.* 145: 641, 1942.
12. Van Slyke, D. D.: *IBID.* 73: 695, 1927.
13. Folin, O.: *IBID.* 101: 111, 1933.
14. Rubicon Company: *Notes on Operation of the Evelyn Photo-electric Colorimeter.* Philadelphia, p. 29.
15. Watanabe, C. K.: *Am. J. M. Sc.* 154: 76, 1917.
16. Steinitz, E.: *Therap. d. Gegenw.* 63: 369, 1922.
17. Berglund, H., and Frisk, A. R.: *Acta Med. Scandinav.* 86: 233, 1935.
18. Gärdstam, R.: *IBID. Supplement* 67, 1935.
19. Brøchner-Mortensen, K.: *Medicine* 19: 161, 1940.
20. Coombs, F. S., Pecora, L. J., Thorogood, E., Consolazio, W. V., and Talbott, J. H.: *J. Clin. Investigation* 19: 525, 1940.
21. Nayar, A. S. M.: *J. Obst. & Gynaec. Brit. Emp.* 47: 404, 1940.
22. Chesley, L. C.: *Surg., Gynec. & Obst.* 67: 481, 1938.
23. Herrin, R. C.: *Physiol. Rev.* 21: 529, 1941.

VAGINAL HYSTERECTOMY IN THE MANAGEMENT OF DESCENSUS UTERI*

W. C. DANFORTH, M.D., EVANSTON, ILL.

(From the Department of Gynecology and Obstetrics, Evanston Hospital)

IN THE management of descensus of the uterus, today, two procedures are employed almost to the entire exclusion of all others. One of these is vaginal hysterectomy together with the use of the cardinal ligaments, the pubocervical fascia, the uterosacral ligaments, and the upper portions of the broad ligaments for the construction of a supporting structure which will uphold the vaginal vault and the bladder. The other is the Manchester operation, or one of its modifications. The latter, as it is usually done, employs the bases of the broad ligaments and the pubocervical fascia as the means of support, the cervix being nearly always shortened by amputation. Advancement of the bladder is an essential part of this operation. The intelligent treatment of uterine descensus requires a clear conception of the mechanics of uterine support and of the anatomy of the structures by which this is accomplished. The use of the round ligaments to hold up the stump of the uterus after subtotal hysterectomy long since demonstrated its ineffectiveness and the attachment of the cervical stump or the fundus of the uterus to the anterior abdominal wall has been an unsatisfactory procedure. To deal efficiently with descensus of the uterus, and the sometimes marked outlet relaxation which accompanies it, requires a greater operative skill and a better knowledge of pelvic anatomy than do many of the operations carried out abdominally.

In either method of operation, the restoration of support depends upon the use of these structures. Failure to use them, or failure to employ them properly, causes the operation to be a failure.

We have treated the greater part of our cases of descensus by vaginal hysterectomy. A smaller number have been dealt with by the employment of bladder advancement, anterior colpoplasty, and transplantation of the bases of the broad ligaments. To this has been added a perineal plastic operation varying in degree according to whether we were dealing with a simple rectocele or an enterocele.

In a little more than 600 vaginal hysterectomies we find that the operation was done for descensus of greater or less degree in 160 cases. All cases have been excluded in which the cervix did not come easily to the introitus with slight traction. These we refer to as descensus of the first degree. There were 36 of these. Those in which the cervix emerged from the introitus for a distance of not more than 2 inches were termed second-degree descensus. Of these there were 65. Those in which the uterus came out further, including those in which the entire length of the uterus came out, are termed third degree. This group numbered 59. In many of the cases of more extensive descensus an unhealthy cervix was found with decubitus, endocervicitis, and eversion. Occasionally small fibroids were present.

So far as technique is concerned, there were two groups of cases. In those in which the uterus was entirely out, or at least a large part of its bulk escaped from the vagina, we have used the method which is often spoken of as the Mayo operation and which has been well

*Presented before a meeting of the Chicago Gynecological Society, Oct. 29, 1911.

described by Ward. The operation as first described has been somewhat modified by Ward. In addition to the method as described by him we have found the use of the pubocervical fascia, dissected free in the early part of the operation and brought together over the united broad ligaments, to be a valuable part of the procedure and one which materially adds to support. An inverted T-shaped incision is made on the anterior wall extending nearly to the urethra.

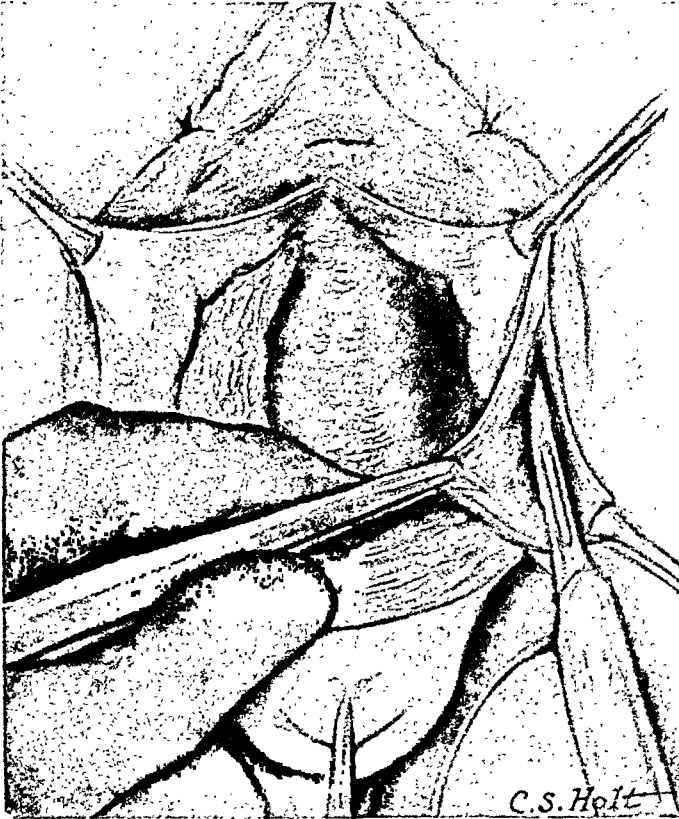


Fig. 1.—Dissection of the fascia of the anterior wall. Dissection complete on left.

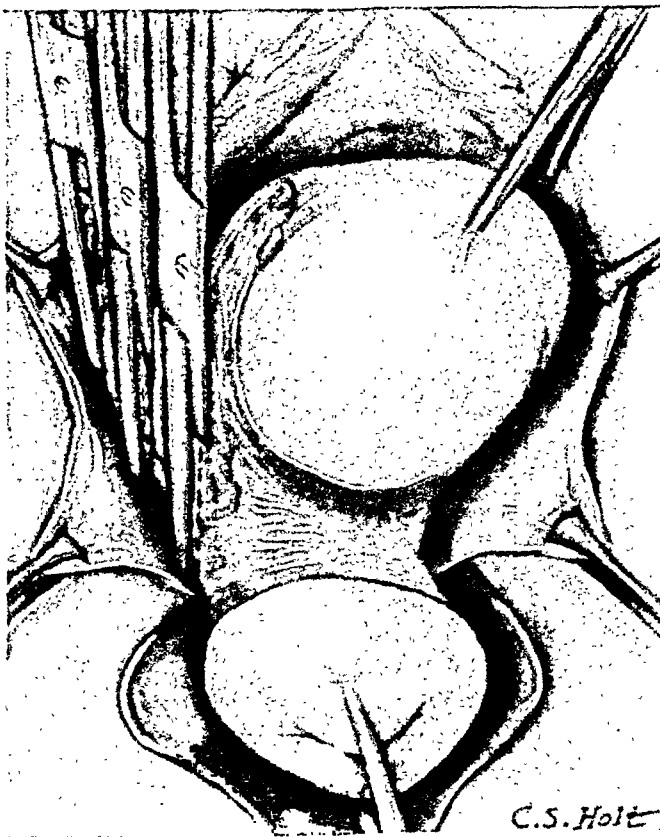


Fig. 2.—Broad ligament caught with three clamps and divided. Uterine artery visible.

Flaps are freed on each side and the fascial layer is carefully dissected free. This fascial flap is important and it should be gotten out as nearly intact as possible. We have tried both scissors and the knife for this step and believe the knife to be the better. The anterior peritoneal fold is then opened. The incision is extended around behind the cervix and the posterior peritoneal pouch is opened. The uterosacral ligaments are caught with short

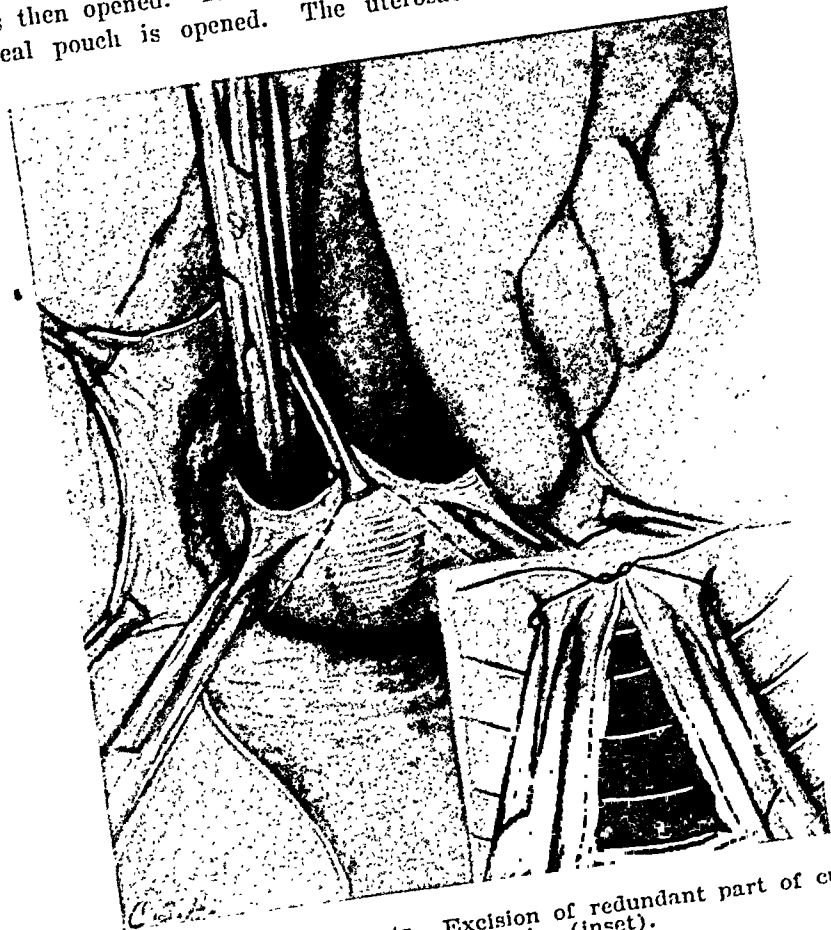


Fig. 3.—Clamps on uterosacral ligaments. Excision of redundant part of cul-de-sac. Closure of posterior hernia (inset).

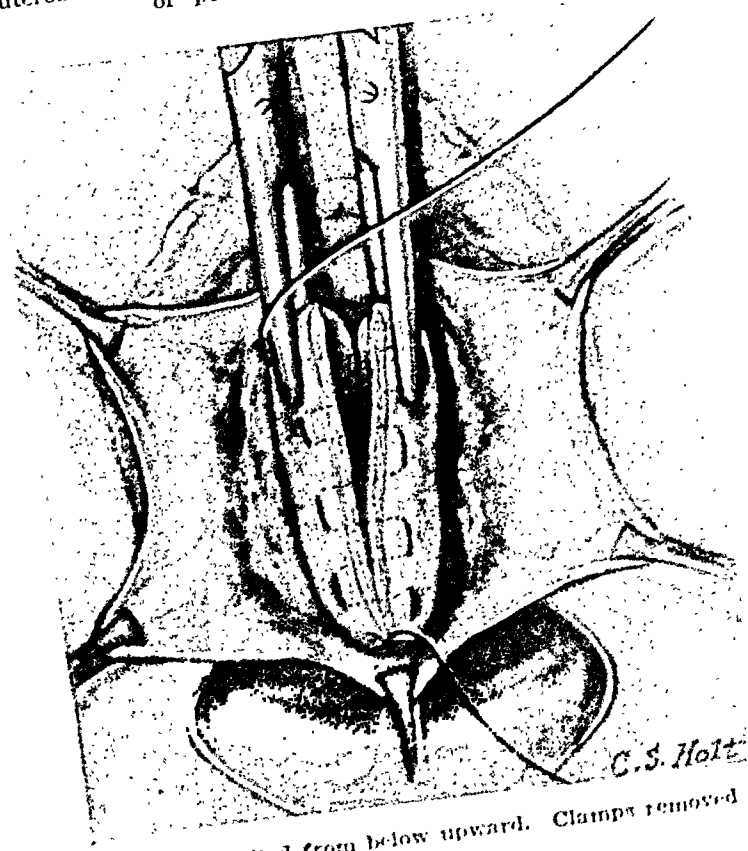


Fig. 4.—Broad ligaments are united from below upward. Clamps removed as future progresses.

straight clamps and divided. The uterus is then turned out anteriorly and the broad ligaments caught in three clamps on either side. The uterus is then removed. The next step is to approximate the uterosacral ligaments. In patients in whom there is a marked enterocele it adds much to the efficiency of the operation to resect a portion of the uterosacral pouch, much as one might remove a part of the sac in a hernia. This step in the procedure was originally suggested by Ward. An efficient closure of the posterior part of the weakened uterine supports is a very important part of the operation. We have found that here is a frequent place for failure to manifest itself. Whether a part of the pouch is removed or not,

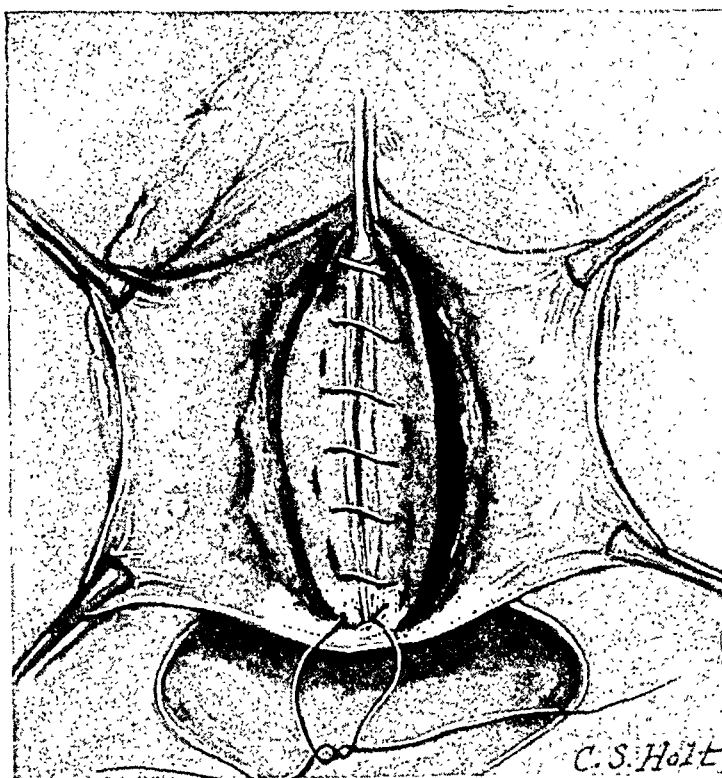


Fig. 5.—Suture returns re-enforcing closure.

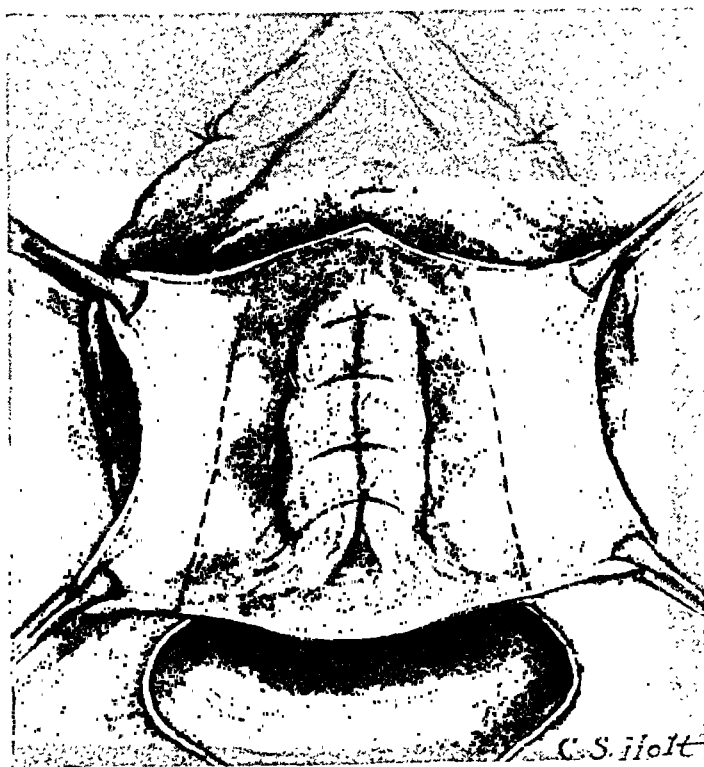


Fig. 6.—Fascial structure united by fine catgut sutures.

the uterosacrals are united with three, or perhaps four, transverse sutures. This closes the posterior part of the weakened area. The broad ligaments are then closed by means of a running mattress suture passed back of the clamps which are removed in succession from below upward as the suture proceeds. This suture is locked at the top and then, in the form of a running suture, is brought back to the point from which it started. This adds to the safety of hemostasis and brings the peritoneal surfaces into better apposition. The anterior edge of the sutured ligaments is then fastened below the rami of the pubes and as close to them as possible by means of a stitch on either side. This is to close the anterior gap and to prevent the bladder from escaping over the forward edge of the broad ligaments. If a gap remains between the uterosacrals and the hammock of broad ligaments, this is closed by suture. A firm floor has then been formed upon which the bladder may rest. Over this is sutured the pubocervical fascia, and, finally, the mucosa is closed after removing the excess portion. The pubocervical fascia and the mucosa are best closed with fine, No. 0 chromic gut used singly. This is fully strong enough and leaves less material to be absorbed. A perineal repair is done, the degree of which depends upon the degree of relaxation. The cure of enterocele depends upon the closure of the uterosacrals rather than upon the perineal plastic. It is essential to be able to distinguish between enterocele and rectocele. We have seen a number of patients in whose cases failure to make this distinction, which has led to an attempt to provide relief by the use of a perineal repair, has resulted in failure.

A variant of this procedure is utilized when the uterus does not come down far enough to be brought entirely out of the vagina. In these cases it does not come far enough out to render the use of the running mattress suture easy. Under these conditions the broad ligaments are caught in clamps, usually three on each side, ligated and divided. The uterus is brought out anteriorly or posteriorly as may seem easier. The ligated ligaments are then united in the median line and the pubocervical fascia is then brought together over them. The closure of the uterosacral ligaments is carried out just as has been described. This last method is well illustrated in the last edition of the textbook of Curtis.

Our experience has led us to emphasize a few points in operative technique. The closure of the posterior hernia which comes down through the interval between the uterosacral ligaments is extremely important. In our earlier cases, before we came to appreciate the necessity of this, we had some recurrences of the enterocele. If the uterosacral pouch of peritoneum is lengthened notably, it should be resected as one would do with a hernial sac. It is essential to close the anterior portion of the weakened area. Thus is accomplished by attaching the sutured broad ligaments, as has been noted above, as high as possible under the rami of the pubes. A careful perineal repair is essential. It is unnecessary, particularly in fascial approximation and in the closure of the mucosa, to use heavy catgut. We find that No. 0 chromic gut is fully heavy enough and believe that it has an advantage in that it leaves less to absorb. For all other work No. 1 gut, used singly, is amply strong. It is illogical to employ gut which has a tensile strength many times that of the tissue in which it is placed. Unnecessarily heavy gut places an unduly heavy burden upon the surrounding tissues as it requires them to dispose of a far larger bulk of material than is needed. The argument that heavy and long-lived gut is needed for hemostasis is erroneous. Thrombosis, upon which permanent hemostasis depends, is complete long before the end of the time needed for the absorption of the gut.

The removal of the uterus is particularly useful in patients in whom the descensus is marked. In our hands, operations of the Manchester type are used as a rule in cases in which the descensus is not too marked and in patients, of whom we have seen a goodly number, who have undergone subtotal hysterectomy elsewhere and in whom the cervix has subsequently come down. It may also be used in cases in which a previous laparotomy renders hysterectomy difficult. Often an incidental condition has been cared for while the existing descensus had been ignored or treated by some inadequate method intra-abdominally. We have also seen a number of patients who had had an attachment of the fundus to the abdominal wall with a subsequent and sometimes very marked descensus.

In many women with marked descensus the uterus is an unhealthy organ. Endocervitis is common, and, if a procedure of the Manchester type is done, after amputating a sufficient length of the cervix, little is left of the uterus. Myomas are often present and, in our laboratory, adenomyosis is sometimes found. The excision of the uterus permits of a more efficient use of the broad ligaments which may be interposed under the bladder, and which, when reinforced by the pubocervical fascia, form an efficient support. In these cases there is always a herniation of the posterior part of the upper pelvic floor. This can be much better dealt with after the uterus is out than when it is not removed. The Manchester operation does not include suture of the uterosacral ligaments. This posterior

repair is one of the most important parts of the operation, and, if not well done, will result in a recurrence in the form of a posterior herniation.

In the fetus the rectouterine pouch extends to the level of the levator ani. This depth decreases with age until the lowest point of the cul-de-sac is at the level of the second or third sacral vertebra. A persistent pouch of the fetal type may predispose to descensus. Descensus which occurs in nonparous women probably is due, at least in many cases, to this congenital condition. It has not been possible to obtain follow-up data concerning all of the patients upon whom this operation was done. Some of them were patients in the ward service and not all of them were altogether cooperative. There were a number whose homes were outside of Chicago, sometimes at a considerable distance, and these could not be accurately followed up. We have felt that letters addressed to patients are not wholly to be relied upon and replies may indicate a result either better or worse than would be revealed by actual examination. Most of them, however, were seen by the member of the staff who carried out the operation. One statement must be made in considering the end result. The type of vaginal hysterectomy done for conditions other than marked descensus need not shorten the vagina. In a large series of these we have found it quite possible to maintain a normal depth. In those done for descensus, especially those in which the uterus has emerged partially or wholly from the introitus, the vagina is already shortened. The descending uterus brings with it the anterior and posterior walls. Shortening has already taken place. In some of these patients there is some shortening after operation. In most of them it is not extensive enough to cause any complaint and many of the patients are elderly women. In many of them shortening is not noticeable. In estimating the value of the end result we have been concerned as to whether the vaginal vault is well supported, the anterior vaginal wall held firmly up, with relief of incontinence if it was present before the operation, and particularly whether the posterior portion of the vault seemed firmly held. Our poor results have ranged from a complete eversion of the vagina, of which there has been but one, to slight relaxations of the anterior wall, causing more or less cystocele or urethrocele.

In the less advanced cases of descensus, those of Group 1, we were able to follow 26 accurately. Success was attained in all but one. In this group of cases the problem is less difficult than in those on which the uterus protrudes and the supporting structures are greatly thinned. The material with which to work is of better quality and a firm support is more easily constructed.

Of the patients making up Group 2, 32 reports were obtained as to the end result. Of these 28 were satisfactory and 4 were not. In one of these the end defect was a urethrocele which the examiner described as small. It could not be called an ideal result inasmuch as some of the anterior repair had not held, yet the patient was quite comfortable.

In cases in which incontinence was a symptom, an attempt to correct this was made, usually by the use of the Kelly procedure. This is easily combined with the anterior colpoplasty.

In Group 3, those in whom the uterus came out more than 3 inches, there were 53 cases in which adequate reports could be had. Of these 38 were satisfactory. As these patients have been more inconvenienced by the descensus than those in which it was of a less advanced type, it is especially desirable to give them relief. In 15 cases failure of greater or less degree occurred, one being a total eversion. This patient was a woman well on in years. The problem was ultimately solved by a colectomy. We have had no experience with the attachment of the vaginal vault to the anterior abdominal wall as advocated by Brady.

In estimating unsatisfactory results we have included all cases in which any degree of cystocele persisted or in which any degree of enterocele was apparent. Most of them were quite comfortable.

The operation has the great advantage of being quite safe. One death occurred in this series, giving a mortality rate of 0.6 per cent. This is the only death in a series of over six hundred vaginal hysterectomies done for all causes. The mortality in the entire number of vaginal hysterectomies is 0.16 per cent. The operation in the more advanced cases of descensus is almost extraperitoneal. It may be done by an experienced operator in less than an hour and is withstood very well indeed even by women of advanced years. It shares this factor of safety with the Manchester operation but has, I believe, the advantage of giving a more complete support inasmuch as the posterior portion of the upper pelvic floor may be dealt with. The competition between the two procedures should be limited, it seems to me, to cases in which the descensus is not extreme, better when the cervix has not passed the introitus. In 12.5 per cent of our cases, or 20 in number, the result was not altogether satisfactory. In 87.5 per cent the result was satisfactory. By this we mean that a good anatomic result was

attained, that is, a flat and well-supported anterior wall, a complete cure of enterocele, and a well-healed perineum. Many women whose operations might permit criticism concerning the anatomic result were quite happy, satisfied, and relieved of symptoms.

Aftercare is quite simple. A vaginal pack is put in for twenty-four hours. This is used less for hemostasis than for support. The abdominal binder after a laparotomy supports the abdominal wall when the patient vomits or strains in any way. The vaginal pack serves a similar purpose. The bladder is emptied by catheter before the patient is removed from the table. Catheterization is done after twelve hours unless the patient complains of discomfort sooner. Thereafter the bladder is emptied every eight hours until she voids spontaneously. When the bladder empties itself, a test catheterization is done to ascertain whether it empties itself completely. If less than 30 c.c. is obtained, the use of the catheter is discontinued. If the amount is greater than this, the eight-hour schedule is maintained until the amount after catheterization is less than 30 c.c.

The convalescence in the majority of these cases is uneventful. Distention is, as a rule, minimal, and in many cases bladder function returns soon after operation. Some bladder irritability may persist for a time after operation, which is due to the dissection of the bladder base from the anterior surface of the uterus. The greatest single discomfort which these patients seem to have is caused by the stitches in the perineum which close only the skin. Morbidity, as reckoned by the standard of the American College of Surgeons, is high. In the entire series we found that 53.3 per cent had fever on two or more days, excluding the first, the temperature rising to 100.4° F. or more. The extensive dissection which is needed, opening up considerable areas, can scarcely avoid giving rise to some absorption. Recovery, in most cases, gave very little trouble.

In one case death occurred. This patient was a woman in whom the protrusion was about 5 or 6 cm. She went through the operation well but got out of bed the first night and was controlled with some difficulty. She developed a pelvic inflammation and shortly thereafter a pneumonia. The latter was the determining cause of death.

Summary

Vaginal surgery requires a definite knowledge of the anatomy of the region in which the procedure is carried out. It also demands a familiarity with the technique of the operations which are done in this field. The specialist in pelvic surgery should be familiar with both the anatomy and technique, for the results of operations for descensus done from below are so much better than those following abdominal procedures that the latter should give way entirely. The safety of the operation done from below is greater and this fact should weigh heavily in the choice of procedure. It is our opinion that vaginal hysterectomy, rather than the procedures of the Manchester type, particularly in cases of extreme descensus, is the operation of choice. In cases in which the descensus is of moderate degree, either will serve. As in many patients the uterus has passed its usefulness, and especially inasmuch as the cervix is often unhealthy, we believe that removal of the uterus has a much larger field of usefulness than the alternate procedure.

636 CHURCH STREET

Discussion

DR. N. S. HEANEY.—When I was asked to discuss this paper the title was given to me as "Vaginal Hysterectomy and Prolapse of the Uterus," and I prepared a discussion along these lines. When I came to the meeting I found that the paper was on "descensus." We do not use the term descensus. The patient has a prolapse when the cervix comes out of the vagina, up to complete eversion of the vagina or procidentia.

In my mind there is no place for the Manchester operation in the treatment of prolapse of the uterus unless it be combined with bladder advancement which is not a part of the Manchester operation. Anybody who adds bladder advancement to the Manchester operation does something that is useful because that is the particular part of the operation that is efficient.

Dr. Danforth has now had one death in something over 600 cases. I have done vaginal hysterectomy ever since I first started to practice and I have taken statistics only during

less than half of my experience. During this week we completed 1,237 vaginal hysterectomies with some three deaths. Had I started when Dr. Danforth did I would have 675 without a death, because we have done 675 since the last death.

Dr. Danforth uses the technique of the Mayo operation. The Mayo operation was described some twenty-five or more years ago and there should have been some improvement found in this length of time.

Dr. Heaney then quoted extensively from a previously published paper ("Vaginal Hysterectomy in Cure of Prolapsus Uteri") in which his method was described.

DR. JOSEPH L. BAER.—We published an article in 1928, the opening paragraph of which was as follows:

"The choice of operation is influenced first by limitations of conditions in the individual patient; second, by the operator's familiarity and perhaps success with particular types of operation; and third, his desire to improve results through the utilization of other methods."

The publication of 1928 showed 11 types of procedure for the cure of prolapse among 220 operations. The interposition operation was employed 91 times, suspension and vaginal reconstruction in fertile women was employed 14 times, the Le Fort operation 14 times, extra-vaginal reposition 13 times, vaginal hysterectomy 7 times. In 1937, 221 operations were reviewed, which showed the shifting trend of our clinic group at Michael Reese Hospital. One hundred sixteen patients were treated by vaginal hysterectomy and only 30 by the interposition operation; 29 by the Le Fort operation, 13 by the Gilliam suspension and parametrial fixation; there were 9 instances with us of the Manchester operation. In 1939, Dr. M. L. Leventhal reported on 51 Manchester operations. We had a veritable rush of Manchester operations because we were all enthusiastic about them. Examining the data for 1944 from January 1 to October 14, we found that vaginal hysterectomy was performed 127 times, the Manchester or parametrial fixation 8 times, the Neugebauer-Le Fort, 5 times, and not a single Gilliam or Kocher extraperitoneal fixation. So we have come to vaginal hysterectomy as the outstanding cure for prolapse.

The essayist has further confused the classification of prolapse. The essayist would have the first degree as that stage in which the cervix can easily be brought by traction to the introitus; the second degree, the condition in which the cervix emerges not over 2 inches; the third degree, with the cervix completely down. In the body of the paper, however, he speaks of Group 3 as those cases in which the uterus is out more than 3 inches.

The alleged purpose of a vaginal pack after operation, is support, and comparison is made to an abdominal binder which supports the recently opened abdominal wall in laparotomy. Of course we know that in spite of an abdominal binder or corset or any other abdominal device, if the patient is going to have an evisceration neither corset nor binder is going to prevent it. By the same token a pack left in the vagina for twenty-four hours, to my way of thinking, is merely a foreign body which serves no useful purpose and interferes with proper drainage of the serum discharge or such bloody discharge as might otherwise escape and not become infected.

The essayist uses eight-hour catheterization technique for the bladder after the first period of twelve hours postoperative. My present leaning is toward a permanent catheter, provided it be a small type which stays in situ without having to be repeatedly reinserted. A catheterization twelve hours after operation is not too long an interval unless the patient is receiving an abundance of parenteral fluids, in which case the bladder is going to be more than full and should be emptied as required.

The essayist's technique is precise, sound, and excellent except for the use of a continuous mattress suture for the control of the uterine artery, which I do not like. I am sure Dr. Danforth is continuing it because so far he has had no disaster, but I submit that disaster will come.

Dr. Danforth mentions 15 failures in a total of 53 cases, a percentage of 28. That is a high percentage of failures to register in a group of women without any subjective symptoms. I am not willing to accept that high percentage of failure as an acknowledgment of failure of his work. In our original report on the interposition operation, we had 12.5 per cent failures, on the basis of which we have practically discontinued the interposition operation.

Dr. Heaney states there is no place for the Manchester operation in prolapse unless bladder advancement be carried out. If he chooses to limit the word prolapse to those instances in which the entire uterus is out, which, of course, is not the connotation of the word prolapse, then I shall not quibble with him. But certainly there is a place for parametrial

fixation in lesser degrees of prolapse and it does not require advancement of the bladder. The Manchester operation is calculated to achieve its result by anchoring the cervix. Irrespective of what one does with the bladder, there is still a place for the Manchester operation. I caution Dr. Heaney against further use of pituitary preparations for the control of bleeding. We have discontinued their use entirely. We have had disturbing conditions on the operating table following the use of pitressin or its modifications.

Finally, Dr. Heaney stressed the importance of bringing the round ligaments down and approximating them in the midline at the maximum tension that can be put on them without avulsing them. Unfortunately those women have a very uncomfortable postoperative course. The traction on the round ligaments is a source of bilateral pain in the groins which persists until the fixation lets go.

DR. ROBERT M. GRIER.—When I first started with Dr. Danforth in 1924 practically all of his hysterectomies were subtotal. The argument for this was that the postoperative mortality was too high in the total operation, due to infection. We used to have a great many women with cystocele, rectocele, and descensus, and for these we usually did a two-stage operation, repairing the cystocele and rectocele with a Sturmdorff operation on the cervix, and then through a laparotomy incision the uterus was removed.

In 1927 Dr. Danforth became quite concerned because of some failures. He tried the interposition operation on patients with severe cystocele, but this was given up. Then, I believe due to the influence of Dr. Heaney, he did more and more vaginal hysterectomies. The question became, how large should the uterus be before the vaginal operation was inadvisable? Now we avoid its use when the uterus is as large as a four month's pregnancy or even less. We do vaginal hysterectomies for those cases where there is a pronounced cystocele and rectocele and the uterus is not too large. The Ward technique came into use and we began to unite the round ligaments under the pubic arch for severe cystocele after doing a vaginal hysterectomy.

Then, I think due to the Mayo Clinic influence, we found we could do total abdominal hysterectomies without as high a mortality as was thought. We now do more of them and reserve vaginal hysterectomies for marked prolapses. At Evanston Hospital we do more total abdominal hysterectomies than any other type but we still do vaginal hysterectomies for procidentia and outlet relaxation. We thus do fewer subtotal operations but a good share of vaginal hysterectomies.

DR. DANFORTH (Closing).—These 600 vaginal hysterectomies cover a period of about ten years. I think that what we term the Mayo operation probably was first done by Riddle Goff but he did not publicize it adequately. Dr. Charles Mayo was the one who made public the worth of the operation and that is why it has his name.

It is interesting to hear Dr. Baer state that in this year's work at Michael Reese Hospital they have come back to vaginal hysterectomy after having given it up for a very considerable time in favor of the Manchester operation.

As to the criticism of the running mattress suture I can only say that we have used it in a large number of cases and have had no bleeding. The only bleeding we have had after total abdominal or vaginal hysterectomy has been bleeding from the vaginal vault.

BILATERAL POLYCYSTIC OVARIES*

Significance in Sterility

IRVING F. STEIN, M.D., F.A.C.S., CHICAGO, ILL.

(From the Michael Reese Hospital)

BILATERAL polycystic ovaries are associated with a definite clinical syndrome, the significance of which is not generally acknowledged by gynecologists. The characteristics of this syndrome are menstrual irregularity featuring amenorrhea, a history of sterility, masculine type of hirsutism, and, less consistently, retarded breast development and obesity. Extreme masculinization is sometimes noted in addition to hirsutism and there may be facial acne. Pelvic pain is not a consistent symptom, but is one which occasionally causes the patient to present herself for examination. The ovaries are similarly and simultaneously enlarged but are difficult to palpate; therefore pneumoroentgenography is of great value in establishing or corroborating the diagnosis. The cure of bilateral polycystic ovaries requires surgical treatment.

It is fifteen years since we first performed wedge resection of bilateral polycystic ovaries for the relief of prolonged amenorrhea and/or sterility. Two previous publications^{1, 2} have been presented. This communication represents the third five-year report on this subject. When we made our first contribution on this subject in 1935, the syndrome associated with bilateral polycystic ovaries was a new concept in gynecology. Since then, we have emphasized its importance in the study of sterility. We stated then, and are still convinced, that the development of this condition is not congenital; neither is it inflammatory nor degenerative. It is the result of a definite endocrine disturbance.

Amenorrhea is a conspicuous feature of the clinical course in these patients. One group never menstruated. Another showed mere staining or a very scanty flow which continued throughout adolescence and which developed into complete amenorrhea. These patients never really menstruated in the physiologic sense but had scant and probably anovulatory bleedings. No true menstrual cycle was ever established in this group. The largest group of patients had secondary amenorrhea and irregular periods.

The amenorrhea is often preceded by a history of normal menstrual cycles which may extend through adolescence and even into early maturity when irregularity and missed periods usually occur. The irregularity may at first be noted as a hypermenorrhea to be followed after variable lengths of time by increasingly longer periods of amenorrhea. These periods may at first consist of lengthening intervals interrupted by scanty uterine flow. Then the interval may be for two, three, or six months, interspersed with an occasional apparently normal menstrual period. Ovulation may occur once or twice a year followed by a normal period. In other cases, as we have previously reported, periods of amenorrhea had been absolute from two to eight years, continuing until surgical correction of the ovarian pathology was accomplished. In rare instances normal sex cycles were initiated at puberty and continued for some years, and even a pregnancy occurred before there was evidence of cyclic disturbances, such as amenorrhea and secondary sterility. In all of the instances described above, the functional disturbances of the reproductive tract were in association with

*Presented before a meeting of the Chicago Gynecological Society, Oct. 20, 1944.

the development of bilateral polycystic ovaries. Where these ovarian changes occurred early in the reproductive life of the individual, uterine hypoplasia was usually found. In the cases of secondary amenorrhea, however, the uterus was normal in size unless the amenorrhea had persisted for long periods (two to eight years) when a definite diminution in uterine size, or even atrophy, occurred. In regard to the secondary sex characteristics, they are of two types: the true feminine, and those which are characterized by masculinizing effects.

Hirsutism occurred in fully 50 per cent of our patients, but it varied a great deal in distribution and extent. In some of the adolescent patients the beard was so heavy that it required frequent shaving and the arms and legs were also markedly hairy. In many cases there was a sternal hairy growth with rings of coarse hair about the areolae of the breasts and a masculine type escutcheon. The vulvar hair was coarse in texture and was thick. Voice changes have not been conspicuous but there were two adolescent patients with marked hirsutism and virilism whose voices were noticeably deep. The feminine type exhibited no abnormal hair distribution.

Breast development varied considerably, from the fully developed feminine type to marked hypoplasia, and there was no definite relationship between breast development and hirsutism. In one case of primary amenorrhea there was practically *no visible breast development*: a mere papulelike elevation represented the nipple. A most remarkable and rapid development occurred in this patient after surgical treatment of the ovaries. The breasts enlarged and the nipples and areolae developed noticeably in a few months. After marriage and the birth of a child, lactation occurred and the patient was able to nurse her child successfully.

Obesity was present in approximately 10 per cent of our patients in this series. At first we had considered this as characteristic of the syndrome, and so stated in our original report. The basal metabolic rate in these patients was always within the normal range, however, and it is likely that obesity is no more common in this than in other gynecologic conditions.

Diagnosis

Bilateral polycystic ovaries are frequently unrecognized on routine pelvic examination as they are difficult to palpate. This may be true because more than one-third of our patients were single girls in whom a digital examination was limited to rectoabdominal palpation, which as a rule is not conclusive. In obese women, and in those who were rigid and tense, or in patients in whom the ovaries were of the "oyster type," palpation proved to be unsatisfactory and a presumptive diagnosis was made until more accurate and reliable methods could be employed. Because of the difficulty encountered in regularly palpating the ovaries in this group of women, gynecography was utilized for diagnosis.

There are very definite clinical indications which lead to the *presumptive diagnosis* of bilateral polycystic ovaries, such as the history of amenorrhea and/or sterility, and the discovery upon general physical examination of a masculine type of hirsutism, and in many instances, hypoplasia of the breasts. Pelvic examination will often reveal the presence of a small uterus. While in some women we can palpate definitely enlarged and globular ovaries, in the great majority we fail to find any abnormality and rely upon pneumoroentgenography. Here in gynecography we have a simple and positive method of diagnosis, so conclusive in its information as to be the deciding factor before laparotomy is performed. It is noteworthy that in every instance where this

diagnostic method was employed and bilateral polycystic ovaries found on the films, corroboration was obtained at the time of surgery.

Gynecography has proved to be the mainstay in diagnosis, not alone for recognition of ovarian enlargements which escape palpation, but also for a true evaluation of the pelvic status. Uterine hypoplasia is often present and is readily recognized by this means. Normally, the uterine shadow upon pneumoroentgenography is about four times the size of the ovarian shadow. In the condition under discussion, however, the ovaries may appear half as large or even the same size as that of the uterus. The ovaries may appear to be round, oval, elongated, or angular on the film, depending upon the position of the gonads in the pelvis at the time of x-ray. It should be noted that the prone, modified knee-chest posture is assumed for the x-ray and the film records a projected shadow from one aspect only (Fig. 1); the ovary may be suspended so that it presents its broad or narrow diameter for projection on the film. Hence, one ovary may appear round and the other oval, and one may appear much larger than the other, even though they are approximately the same size. The bilateral and symmetrical involvement of the ovaries is in itself a valuable diagnostic sign. Interpretation of the film requires experience (Figs. 2 to 7).



Fig. 1.—Hypoplastic uterus. Bilateral symmetrical involvement of ovaries. Difference in shape and size on film due to lateral and end views. Diagnosis: Bilateral polycystic ovaries.

For purposes of establishing tubal patency or obstruction, and for abnormalities of the uterine cavity, hysterosalpingography (utilizing opaque media) is valuable, but pneumoroentgenography is superior for recognition of ovarian and uterine enlargements. The two methods just referred to comprise gynecography.³

Earlier in our study, the basal metabolic rate was frequently estimated, especially in those cases where obesity was present, but as it was found to be within normal range in all of these patients, it was no longer considered of diagnostic value. In a considerable group of our patients, routine vaginal

smears and endometrial biopsies were taken. In cases of prolonged amenorrhea, the vaginal spreads showed a typical menopausal pattern for the most part. The biopsies as a rule revealed no significant data. It was difficult to determine when the biopsy should be obtained, inasmuch as the cycles were irregular and in some cases absent. If the biopsy were taken at the beginning of what proved to be a normal period, it would reveal a secretory phase, inasmuch as occasionally, perhaps once or twice a year, ovulatory cycles did occur. We are

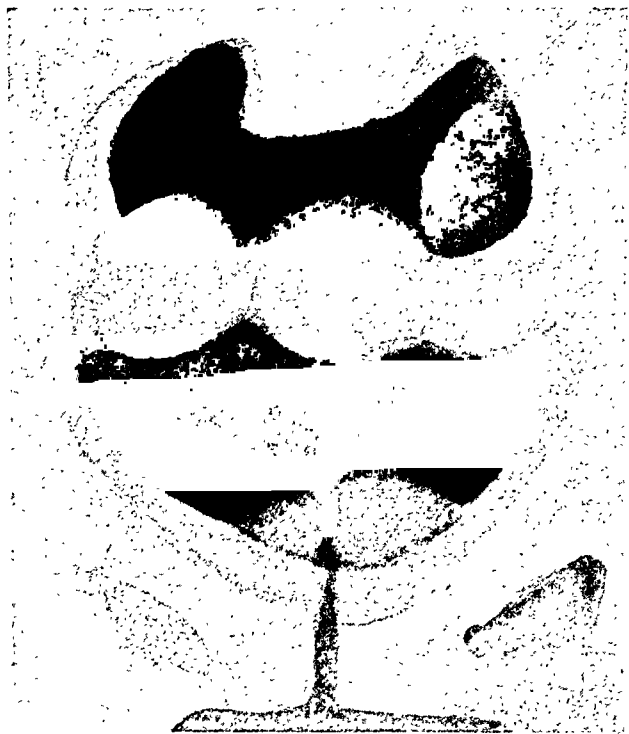


Fig. 2.—Hypoplastic uterus. Bilateral symmetrical involvement of ovaries, equal size and shape. Diagnosis: Bilateral polycystic ovaries.

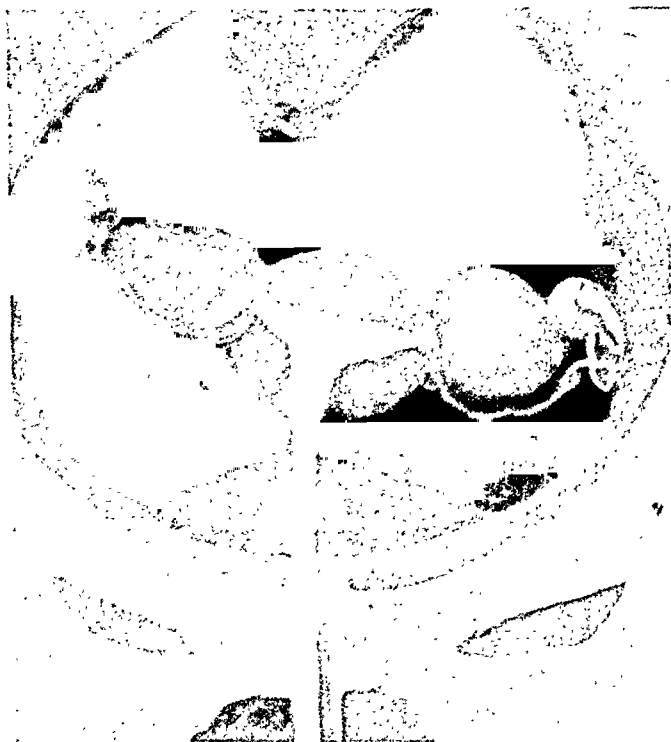


Fig. 3.—Combined gynecography. Bilateral symmetrical involvement of ovaries (each about $\frac{2}{3}$ size of uterus). Diagnosis: Bilateral polycystic ovaries.

convinced, however, that most cycles in patients with bilateral polycystic ovaries are of the anovulatory type, as evidenced by the histories of menstrual irregularity and the long periods of sterility. Sugar tolerance tests and x-rays of the pituitary were done in a number of our earlier patients but no findings of significance were obtained.

Summarizing, the most significant data in establishing a diagnosis are: a history of primary or secondary amenorrhea; a history of sterility; a male



Fig. 4.—Hypoplastic uterus. Bilateral symmetrical involvement of ovaries. Diagnosis: Bilateral polycystic ovaries.

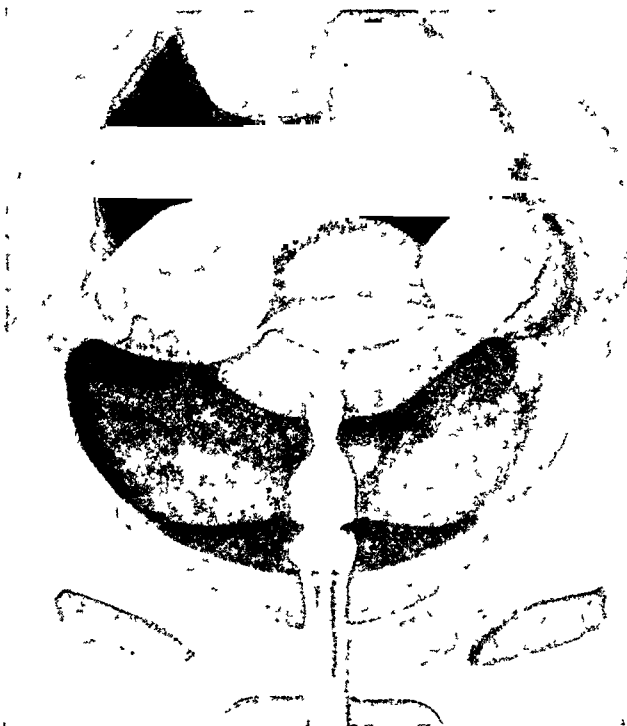


Fig. 5.—Combined gynecography. Bilateral involvement of ovaries. Right ovary larger. Uterus and tubes normal. Diagnosis: Bilateral polycystic ovaries.

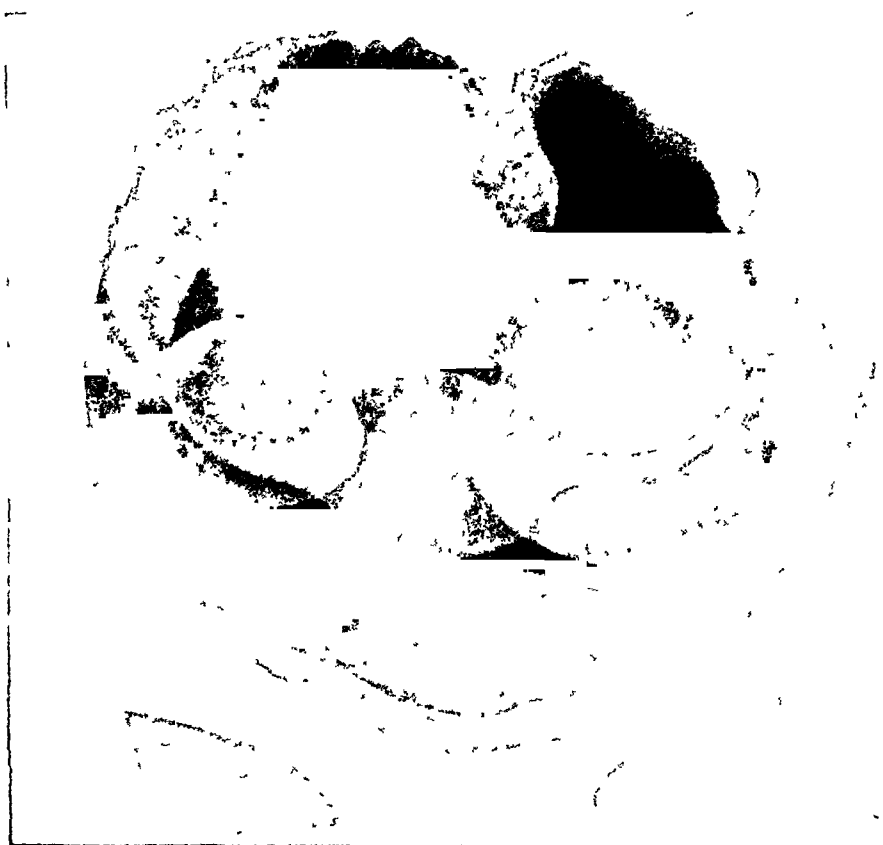


Fig. 6.—Hypoplastic uterus. Bilateral ovarian involvement. Left ovary larger. Diagnosis: Bilateral polycystic ovaries.



Fig. 7.—Hypoplastic uterus. Typical symmetrical ovarian enlargement. Diagnosis: Bilateral polycystic ovaries.

type of hirsutism; breast changes; and the finding of bilateral ovarian enlargements (corroborated by gynecography).

In the past fifteen years, we have studied 53 patients in whom the diagnosis of bilateral polycystic ovaries has been made, corroborated by gynecography and treated by bilateral ovarian wedge resection. These patients consisted of 23 single and 30 married women. Of the 23 single girls, amenorrhea occurred in 19, irregular bleeding in 3, hirsutism in 13. Four of them complained of pelvic pain. In only 2 was obesity present. In the married group, 24 of the 30 women complained of amenorrhea, 2 had irregular bleeding. *22 presented themselves because of sterility.* Hirsutism was found in 12, obesity in 4; only 8 in this group complained of pain (Table I).

TABLE I. ANALYSIS OF SYMPTOMS AND FINDINGS

NO.	STATUS	AMEN- ORRHEA	BLEED- ING	STERIL- ITY	HIR- SUTISM	PAIN	OBESEITY	X-RAY GYNECOGRAPHY*	OPERATIVE FINDINGS
23	Single	19	3	0	13	4	2	22 B.P.O. 1 Myoma	23 B.P.O.†
30	Married	24	2	22	12	8	4	26 B.P.O. 4—No X-ray	30 B.P.O.† 1 Myoma 1 Granulosa

*Pneumoperitoneum.

†B.P.O. = Bilateral polycystic ovaries.

In analyzing our findings, of the 23 single girls gynecography was obtained in all but one case. Twenty-two showed bilateral polycystic ovaries, one in association with a small myoma (history of bleeding). One film was not diagnostic. Bilateral polycystic ovaries were found at operation in all of the 23 patients. Six had received hormone therapy previously without benefit. In all 23, menstrual cycles were established postoperatively. Usually a normal monthly rhythm occurred and the secondary sex characteristics were definitely influenced, favoring the feminine type. In some of the cases, however, the cycles in the first year following operation were irregular and sometimes prolonged. In three of the patients, inflammatory adhesions occurred with development of a cyst in one ovary. However, *the original condition of bilateral polycystic ovaries did not recur in any case.*

In the married group, 26 of the 30 diagnoses were verified by gynecography. At laparotomy, bilateral polycystic ovaries were found in all of the 30 women, one of whom had an associated myoma and one a granulosa-cell tumor. Ten women had previous hormone therapy with no improvement. After bilateral ovarian wedge resection, all of the 30 women had re-establishment of the menstrual cycle. There were no recurrences in this group (Table II).

TABLE II. ANALYSIS OF TREATMENT

NO.	STATUS	MEDICAL		SURGICAL	
		HORMONE	RESULTS	RESECTION	RESULTS*
23	Single	6	Negative	23	Positive
30	Married	10	Negative	30	Positive

*See Table III.

For ultimate evaluation of the surgical treatment of this condition, the restoration of the reproductive function, particularly in those patients who complained of sterility, is paramount. Of the patients who were single at the time of the ovarian wedge resection, three were subsequently married, all became pregnant, one of them giving birth to two children. Twenty-four of the married women had regularly recurring menstrual cycles, four were irregular, and in two

there was no follow-up. Among the 28 who were followed, 17 of the patients became pregnant. There were 31 women (28 from the married group and 3 from the single group who subsequently married) who were endeavoring to become pregnant. Twenty patients (64.5 per cent) became pregnant, resulting in 26 pregnancies and 28 babies; four were pregnant twice; one was pregnant three times; there were two sets of twins (Table III).

TABLE III. RESULT OF SURGICAL TREATMENT

NO.	STATUS	MENSES		NO. OF PATIENTS PREGNANT	TOTAL PREGNANCIES	RECURRENT CYST
		REGULAR	IRREGULAR			
23	Single	15	4	3†	4	3*
30	Married	24	3†	17	22	0
Total			4		2 sets of twins	
53§		39	2†	20	26 preg.	3
			8		28 babies	

*Inflammatory adhesions—cyst.

†No follow-up.

‡Subsequently married.

§60 (7 additional operations).

We repeat, for emphasis, that in no case was there a recurrence of bilateral polycystic ovaries. In 3 women in the single group, however, a unilateral cyst of inflammatory origin occurred, causing pain and menstrual disturbance.

Discussion

The normal sex cycle is dependent upon the harmonious interaction of the pituitary gland, the ovaries, and the other glands of internal secretion. Physiologically, ovulation occurs periodically and usually at a monthly rate, beginning at puberty and ending with the menopause. It is generally believed that ovulation occurs alternately when both ovaries are present, and if one ovary is removed, the monthly cyclic process continues in the remaining ovary. As there are probably two or three hundred thousand primordial follicles in the ovaries at birth and only one comes to maturity about the time of puberty and monthly thereafter, there is a sort of order or succession in which the follicle is sensitized and responds to anterior pituitary stimulation. When the endocrine function is disturbed and hypersecretion of the pituitary occurs, it is possible that a number of immature follicles may be simultaneously stimulated in both ovaries and that this process may result in an accumulation of multiple cystic follicles in the ovarian cortex. The prepubertal ovary appears somewhat similar but lacks the pathologic aspects of bilateral polycystic ovaries; in the group of young women who have never menstruated, there may be a continuation of the prepubertal state, i.e., amenorrhea and immature secondary sex development as a result of hyperpituitary effects upon the ovary. This eventually produces the typical pathologic effect in the ovaries. In women who apparently developed normally at puberty and during adolescence and in whom secondary amenorrhea occurred, the development of multiple follicle cysts in the cortex of both ovaries gradually transforms the ovaries into enlarged, smooth, and typically polycystic gonads. In both instances, normal function such as ovulation is suspended, or at best, occurs but rarely. Hence, amenorrhea and sterility usually obtain.

Both amenorrhea and uterine bleeding may, according to Zondek,⁴ be due to hypersecretion of the anterior lobe of the pituitary gland with no correspondingly characteristic lesion of the ovaries. If this stimulation con-

tinues over a long period of time, eventually histological changes appear in the ovaries, characterized by multiple follicle cysts, a thickened capsule, and an increased fibrosis of the stroma of the ovaries. The cysts vary in size from a few millimeters to 1 centimeter in diameter, and may be lined by a single layer of granulosa cells, but the more advanced ones are lined only by theca cells. The cysts are usually limited to the cortex and, although almost always filled with an estrin-containing liquor, are usually functionless. There is probably no absorption of estrin from these cystic follicles which have become pathologic. If corpora lutea are found, they are few in number, as there are seldom normal Graafian follicles which come to full maturity. Therefore, the surface of the ovary, instead of being irregular with contracted corpora albicantia, is smooth, pearly gray in color, and contains small telangiectases.

In all women there are both estrogenic and androgenic effects from the ovary. Normally the estrogenic is sufficiently excessive to counterbalance any androgenic effect there may be. Hence the usual feminine secondary sex characteristics. When the estrogen-androgen balance is upset, there may be an inhibition of feminizing effects, and when the androgenic secretion is excessive, definite masculinizing effects result. This is evidenced by the masculine type of hirsutism and, in some cases, by virilism.

The fact that ovulation rarely if ever occurs in patients with well-developed bilateral polycystic ovaries may be explained by a mechanical theory. The enlarged and increased number of cysts crowding the ovarian cortex and covered by a thick ovarian tunica may, by pressure, prevent the primordial follicles in the stroma from maturing and secreting their hormones. If rupture of the Graafian follicles does occur, it may do so into an adjacent follicle rather than through the thickened capsule of the ovary. Furthermore, a fibrosis of the tunica and stroma compresses and obliterates the blood vessels which normally would carry the hormone secretions (Levine⁸).

After changes in the ovary have been established, hormone therapy is of no benefit. It is our belief that the good results in cases of amenorrhea, such as reported by Frank et al.,⁵ Rubin,⁶ Kaplan,⁷ and others, have been obtained in patients in whom the ovarian changes had not yet reached the stage of cystosis. At least none of these authors has demonstrated, either by gynecography, surgery, or otherwise, that the patients whom they successfully treated with hormone or x-ray therapy had bilateral polycystic ovaries. We furthermore would like to emphasize that a differential diagnosis should be made utilizing gynecography, to exclude bilateral polycystic ovaries, before treatment for amenorrhea and/or sterility be administered medically (hormone, x-ray, vitamin therapy, etc.).

In our second publication,² we presented case abstracts and described in detail the pathology found in the ovary. Inasmuch as there is a great similarity in the additional cases which we are reporting at this time, we believe it unnecessary and of no increased value to the contribution to add these data. Therefore, we are summarizing the entire fifteen years' series which we have studied and followed.

We have shown in our previously reported 28 patients who were treated by bilateral wedge resection of the ovaries that physiologic function was restored by surgical means, as evidenced by the return of periodic menstruation and by a considerable number of pregnancies. We now submit data obtained from an additional 25 cases similarly treated to substantiate our thesis.

Surgical Treatment

The surgical technique of ovarian wedge resection for bilateral polycystic ovaries is as follows:

A Pfannenstiel incision is made and the enlarged ovaries are delivered into the operative field. Retractors may be removed and lap pads are not required in the peritoneal cavity. The ovaries are separately and successively held by means of a Scudder clamp covered with rubber tubing. A wedge is dissected from the ovary by sharp dissection, the size of which is determined by the amount of ovarian enlargement. The follicle cysts remaining in the ovary are punctured from within the ovarian incision, and tension is thus released. With No. 00 plain catgut, and a fine, full-curved, nonecutting needle,

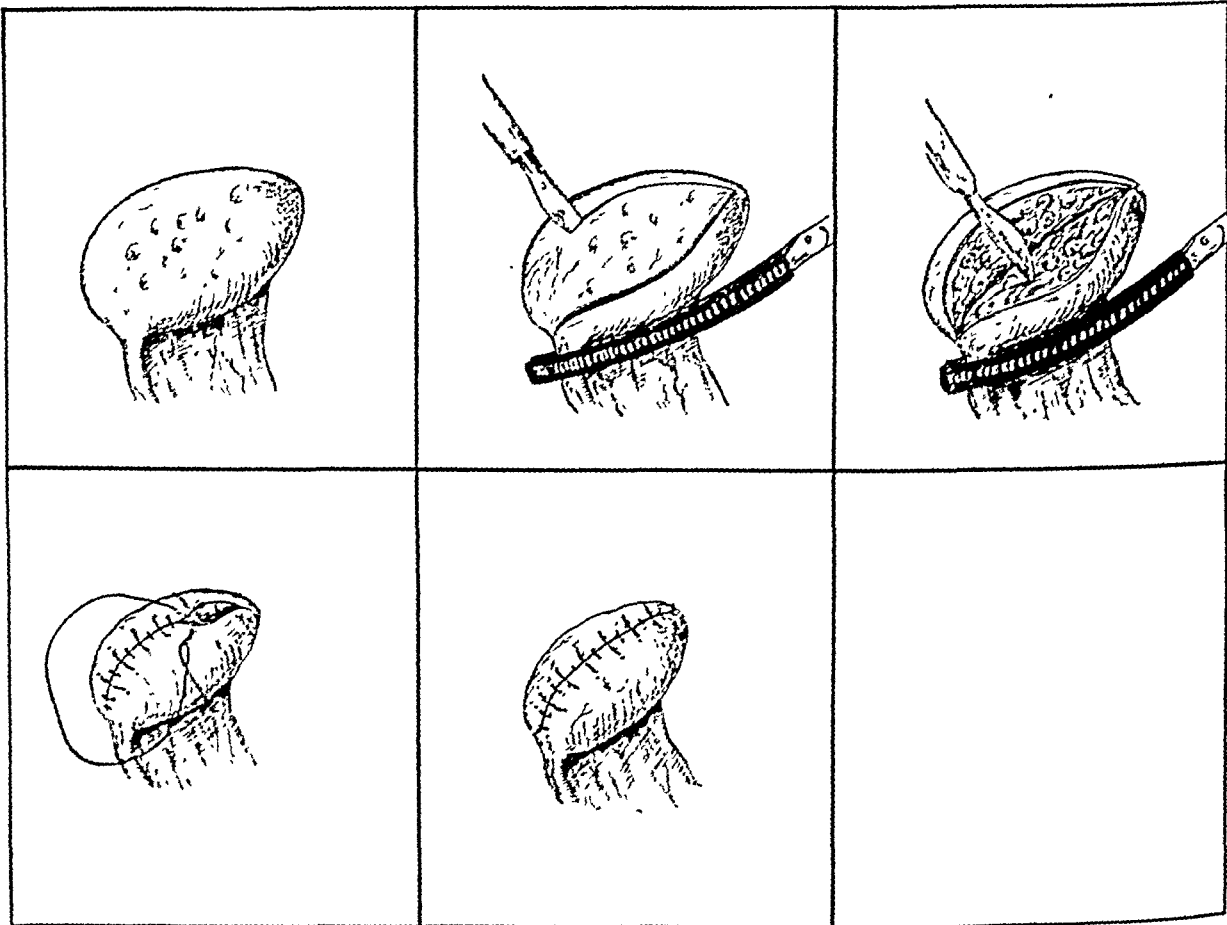


Fig. 8.—Technique of wedge resection of ovaries.

two rows of continuous sutures are used to close the wedge, the first row deep to the base of the wedge, locked at the end, and returned as a second superficial approximation suture (Fig. 8). This leaves a single line scar. The clamp is removed, care being taken that compression of the ovarian vessels by the clamp lasts no more than twenty minutes (usually less than ten minutes is sufficient). Should there be bleeding, additional interrupted sutures insure hemostasis. Recently, we have introduced 5 Gm. of powdered sulfanilamide into the pelvis before closure, and we place the omentum between the sutured ovaries and the intestines. Closure of the abdominal wound proceeds as usual. The entire operation requires between thirty and forty minutes.

Results of Surgical Treatment

We have observed that when the ovaries have been resected, the physiologic sex cycle is resumed. Ovulation, which had been absent for periods

varying from a few months to several years before resection, takes place periodically. This has been satisfactorily shown clinically by carefully kept calendar records and in some instances by vaginal spreads, endometrial biopsies, and most significantly, by the occurrence of pregnancies.

Follow-up pelvic examinations have been made routinely and all except five patients have been followed for long periods of time; some for as long as ten to fifteen years. Following resection, there was a notable improvement, showing feminizing effects upon the individual. The breasts developed markedly, especially in those young women with primary amenorrhea and in whom the breasts were formerly immature. The uterus, which often was found to be hypoplastic, increased measurably in size within six months following surgery. There was distinct improvement in the patients' mental attitude, from one of frustration and sometimes depression, to one of cheerfulness and buoyancy. The tendency to obesity and acne rapidly disappeared.

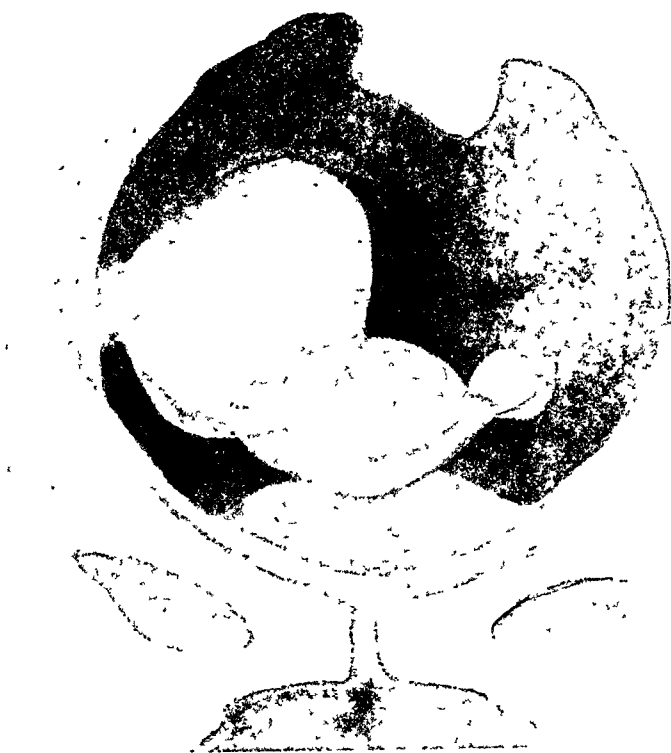


Fig. 9.—Asymmetrical involvement. Lutein cyst of right ovary one year after wedge resection.

The only sign to persist, more or less, was that of hirsutism. It was noted that after ovarian resection the hirsutism no longer increased in amount and distribution; in some instances, the hair on the abnormal sites appeared to lose its coarse texture and gradually become less evident. There was distinct evidence of feminization but no complete disappearance of the masculine hairy distribution which had already become a fixed pattern. It is our impression that this is the most persistent of the abnormal effects of bilateral polycystic ovaries.

As shown in the tables, there were no recurrences of typical bilateral polycystic ovaries in any patient treated by bilateral wedge resection. In one patient who complained of primary amenorrhea, menstruation was restored but it was irregular and later became excessive. She then complained of pelvic pain and it was found that a cyst had developed in one ovary (Fig. 9). A second laparotomy revealed an hemorrhagic corpus luteum cyst with adhesions to the omentum and bowel. In each of the other two girls, a simple cyst developed which required a second operation. In none of these, however, was there a recurrence of typical bilateral polycystic ovaries.

Summary and Conclusions

1. In the past fifteen years, we have studied 53 patients with bilateral polycystic ovaries.

2. These patients sought advice chiefly because of amenorrhea, sterility, and/or hirsutism.

3. The diagnosis of bilateral polycystic ovaries was usually based upon a typical clinical syndrome and was substantiated by demonstrating the ovarian lesions with gynecography (pneumoperitoneum).

4. Hormone and other medical therapy proved valueless in the treatment of this condition.

5. Surgical treatment in the form of bilateral ovarian wedge resection and suture of the ovaries has proved to be a satisfactory and most successful method of treatment.

6. Fifty-three patients were treated surgically. Seventeen married patients and three of the single patients who subsequently married (a total of 20)* became pregnant after operation (64.5 per cent), resulting in 26 pregnancies and 28 babies. This number was obtained as four women were pregnant twice, one three times, and there were two sets of twins.

7. Periodic checkup postoperatively revealed that there were no recurrences of bilateral polycystic ovaries. Three single women who had febrile and painful postoperative courses developed a unilateral ovarian cyst with adhesions (5 per cent).

8. On the basis of our study, we recommend that bilateral polycystic ovaries associated with amenorrhea, sterility, and/or hirsutism, be treated by bilateral ovarian wedge resection.

Since compilation of statistics for this paper, seven additional patients have been treated by bilateral ovarian wedge resection, bringing the total to 60.

I wish to acknowledge gratefully the assistance of Dr. Paul Steinhart, Miss Margaret Weis, R.N., and Miss Paula Bennett in preparing this report.

References

1. Stein, I. F., and Leventhal, M. L.: *AM. J. OBST. & GYNEC.* 29: 181, 1935.
2. Stein, I. F., and Cohen, M. R.: *AM. J. OBST. & GYNEC.* 38: 465, 1939.
3. a. Stein, I. F.: In Davis, C. H.: *Gynecology and Obstetrics*, Vol. III, Hagerstown, Md., 1933, W. F. Prior & Co.
b. Stein, I. F.: *S. Clin. North America*, February, 1943.
c. Stein, I. F., and Arens, R. A.: *Radiology* 15: 85, 1930.
4. Zondek, B.: *Harefuah* 14: 12, 1938.
5. Frank, R. T., Goldberger, M. A., Salmon, U. S., and Felshin, G.: *J. A. M. A.* 109: 1863, 1937.
6. Rubin, I. C.: *Ibid.* 12: 76, 1926.
7. Kaplan, I. I.: *Ibid.* 34: 420, 1937.
8. Levine, R.: Personal communication.

Discussion

DR. EDWIN F. HIRSCH.—Realizing an hormonal imbalance of function in the glands of internal secretion in this disorder, notably the pituitary and the ovaries, Dr. Stein and his associates have studied the effects of wedge excisions of the ovaries, and have accumulated evidence to indicate that this operation does relieve the associated amenorrhea and sterility.

How this operation accomplishes the results obtained has interest. It apparently corrects a disarranged interrelated cycle of ovarian and pituitary glands. Since the changes of the ovarian tissues are in the direction of retrogression and atrophy, the complemental substance of the pituitary gland needed for the luteinization of the theca interna cells of the follicles and the further growth of the corpus luteum may not be stimulated to the functional level. Another possibility is that the effects on the follicle tissues of the ovary are in-

*There addition of pregnancies reported in this group since presenting this paper, and bearing a total of 28 equals 24 + 4 thus pregnant, or 72.7 per cent.

effective because of local nutritional or fluid circulation factors. The edema of the stroma in these polycystic ovaries suggests that such a disturbance is present and that pressure effects are concerned, that may be relieved by the wedge resection of the ovaries. The tissue changes in the ovaries seem to move in a vicious circle. The more chronic the condition the less hope there is for functional recovery by surgical operation. Theoretically, the release of pressure within the ovaries may be beneficial because of an enhanced venous or lymph drainage or an increased arterial blood supply.

DR. RICHARD A. LIFVENDAHL.—All of us seeing the pictures presented by Dr. Stein will assume that we should be able to palpate ovaries that are as large as these. We wonder if it is necessary to visualize these ovaries before operating and whether there is any risk to the patient from pneumoperitoneum. Out of 28 cases from 1935 to 1939 Dr. Stein examined 17 patients who had enlarged ovaries on palpation. Out of the 28 there were four that were indefinite and six were negative to palpation but positive to x-ray examination. Another advantage to x-ray examination is that the x-ray will help to convince the patient that something should be done about polycystic ovaries.

Another question concerns the associated pathology. Dr. Stein reports that six of the cases had an additional lesion such as cystadenoma, granulosa-cell tumors, considerable fibrosis, etc. My experience has been the same. A fibroma and a dermoid no larger than a centimeter in diameter have been found in the ovaries I have examined.

DR. EDWARD ALLEN.—I remember particularly one case that I reported to this Society of amenorrhea of twenty-four years' duration in which we resected the ovaries and took out wedges. These ovaries were one-third normal size. Sections showed no evidence whatsoever of any ova, and yet within a month this patient menstruated and the uterus enlarged. Later, she married and I think she became pregnant, though I did not see her at that time. Her uterus is now five or six times the size it was at the time of operation. On the basis of that case and Dr. Stein's report I have resected seven ovaries bilaterally through the cul-de-sac. They were all grossly normal ovaries. Five pregnancies rather quickly followed although these patients had had all kinds of sterility treatment for from three to seven years without results. This raises the question in my mind whether the cysts are important or whether it is not a mechanical thing entirely. It may work on the same basis as dilatation of the cervix, obviously not because we enlarge the canal but just due to the mechanical effects which change the balance of the hormones affecting the pelvis.

DR. N. S. HEANEY.—It is interesting that in an article on polycystic disease of the ovary and its relationship to sterility, there should be 23 unmarried women from whom you could not expect to get proof of your results. If I were preparing a paper on sterility, one of the first requirements would be patients who could get pregnant. It makes it hard to evaluate your work to put in a group of unmarried women. It is striking, however, that in the 30 cases of married women, 26 pregnancies occurred, with 28 babies.

Years ago we resected polycystic ovaries for various reasons and I have given it up, but Dr. Stein's results certainly give one reason to ponder.

DR. STEIN (Closing).—Of the single women three later married and all had babies. The reason they were operated upon was because they had long periods of amenorrhea and polycystic ovaries. Many of these girls were nurses in training and were referred because of menstrual disturbances. In this group particularly, where vaginal examinations were not done in accordance with training school policy, we found the x-ray a very accurate method of diagnosis.

In answer to the question of danger in inducing pneumoperitoneum, we have employed gynecography for twenty years, and all the members of the hospital and clinic staff and many residents participated in it; we have never punctured a bowel or had a death from shock. I do not know why there has been the obvious lack of interest in the method outside of Michael Reese Hospital. However, if you go back twenty-five or thirty years, you will find that the men who studied tuberculosis were very much averse to using roentgenography because they feared injury to the chest. It took them a long time to be convinced that the x-ray was safe and would show something more than they could discover by other means. Resistance to new methods has been the same with every special group. Gynecography is one of the methods which has proved very valuable, particularly where there has been a difference of opinion. It has proved to be a safe and accurate method in our hands.

Dr. Lifvendahl asked about how many patients who were x-rayed did not show ovarian enlargement. I could not answer that question because we only reported those that did show enlargement and in whom the diagnosis was established. However, even when we palpated the ovaries, we used x-ray for corroboration. In some cases we had to use it as a diagnostic method because we could not palpate the ovaries. We used the x-ray either for corroboration of the diagnosis or where we had made only a presumptive diagnosis.

The associated lesions found in the ovary as a rule were described as microscopic, not macroscopic. It is true that in almost any ovary that you resect you will find little elements, small fibromas on the surface, or some other pathologic structure in the ovary.

I think Dr. Allen's procedure through the cul-de-sac is interesting. Dr. Zondek has punctured a number of bilateral polycystic ovaries through the cul-de-sac. In a former presentation I mentioned a method of splitting the ovary and turning out without sewing, and of decortication which was done in Cleveland by Reycraft. I think the best methods are the completely surgical techniques. There is more danger of adhesions when the incision is not accurately sutured.

MANAGEMENT OF PLACENTA PREVIA

A Twelve-Year Study

HERVEY C. WILLIAMSON, M.D., AND ARTHUR V. GREELEY, M.D.,
NEW YORK, N. Y.

*(From the Department of Obstetrics and Gynecology of the New York Hospital and
Cornell University Medical College)*

THE purpose of this study is to analyze the results of our present methods of treatment of placenta previa and to indicate by what means we may achieve further improvement in the treatment of this serious obstetric complication. A review of the literature shows that there has been marked improvement in the fetal and maternal mortality figures for the treatment of this condition in the past twenty-five years. The use of cesarean section for placenta previa has been demonstrated to be one of the most important factors for this improvement. Prior to the use of this method, which is relatively modern, a maternal mortality rate of 10 per cent and fetal mortality from 50 to 60 per cent was considered satisfactory. Following the judicious use of cesarean section the fetal and maternal mortality rates were immediately reduced. Another important contribution to the improvement in results, particularly in lowering the maternal mortality rate, is the use of blood transfusion. A third factor which we would like to emphasize, that has been responsible for bettering the results, is the discarding of an old tradition in obstetrics, namely, that placenta previa patients must be delivered immediately.

Our present routine for the treatment of patients with vaginal bleeding in the last trimester of pregnancy is as follows: Following a routine vaginal preparation the patient is sent to the delivery floor for observation. Blood typing and cross-matching is carried out. Unless forced to do so earlier by continued profuse vaginal bleeding, the patient is taken to the operating room on the fourth day following admission, where a sterile vaginal examination is carried out. If central placenta previa is found, cesarean section is the treatment of choice, while in the marginal as well as in some of the partial cases an attempt is made to control the bleeding by simple rupture of the membranes. However, the treatment for all types may be influenced by the parity of the

patient, the duration of the pregnancy, the amount of bleeding, and the condition of the patient and the fetus. If the viability of the fetus is questionable, the cervix closed and firm, and there is little bleeding, the patient may be returned to the delivery floor where she may continue to be observed for a much longer period. It should be noted that at the time of examination the operating room has been prepared for immediate cesarean section or insertion of a hydrostatic bag, so that treatment may not be delayed should increased vaginal bleeding be encountered. If cesarean section is decided upon, the type of operation and the choice of anesthesia are dependent upon the preference of the operator.

This report is based on the study of 162 cases of placenta previa in which the diagnosis was made either by vaginal examination prior to delivery or by noting the placental location at the time of cesarean section. Since there were 40,862 cases delivered in the Woman's Clinic of New York Hospital during the twelve-year period of this study, the incidence of placenta previa in this series is 1 in 252.

Table I shows that there were 60 cases in the marginal group, 30 of the partial variety, and 65 central. There were 7 cases in which the type was not determined. Since 6 of the 7 were delivered by cesarean section, it probably indicates the difficulty which is often encountered in making an accurate diagnosis of the type of placenta previa at this time. There was one twin pregnancy in the group. Two patients were also diagnosed as having premature separations of the placenta at the time of admission. In both cases the separation of the placenta was extensive enough to result in the intrauterine death of the fetus prior to the onset of labor. In one patient the diagnosis of placenta previa was made in her second and third pregnancies which occurred four years apart. A low flap cesarean section under local anesthesia was performed on both occasions and each time the diagnosis of central placenta previa was made. There were two other patients who gave a history suggestive of a placenta previa in previous pregnancies which were delivered elsewhere. One of these patients had been induced at eight months because of vaginal bleeding, and in the other case a cesarean section had been performed for central placenta previa.

TABLE I

TYPE OF PLACENTA PREVIA	NUMBER OF CASES
Marginal	60
Partial	30
Central	65
Unclassified	7
Total	162

Table II shows only 161 cases as one patient died before delivery. It demonstrates that in the patients who were delivered, 50 had had no previous viable pregnancy, while 111 had had one or more such pregnancies. This figure is increased to 112 when the patient who died before delivery is included. It also shows that 84 patients were delivered vaginally and 77 by cesarean section. The figures are particularly interesting in the central placenta previa group where it is seen that only 12 of the 65 cases were delivered vaginally and of the 22 primiparas only one was delivered by this route.

TABLE II

	MARGINAL		PARTIAL		CENTRAL		UNCLASSIFIED		TOTAL	
	PRIM.	MULT.	PRIM.	MULT.	PRIM.	MULT.	PRIM.	MULT.	PRIM.	MULT.
Vaginal delivery	10	37	8	16	1	11	0	1	19	65
Cesarean section	5	8	4	1	21	32	1	5	31	46
Total	15	45	12	17	22	43	1	6	50	111
	60		29		65		7		161	

Table III shows the changes in the trend of treatment for the twelve-year period. The total number of cases for each year is listed, then the number of Voorhees' bag insertions, and the number delivered by cesarean section. The entire twelve-year period is then

divided into three separate periods to show the decreasing use of the hydrostatic bag and the increasing incidence of cesarean section. In the first period the bag was used in 44.1 per cent of the cases. This decreased to 26.8 per cent in the second period, then to 15.8 per cent in the last four years. The incidence of cesarean section on the contrary has changed from 30.9 per cent in the first period to 53.6 per cent in the next period, and finally to 68.4 per cent in the last four years. Of the total number of cases the Voorhees bag was used in 31.5 per cent, and 47.5 per cent were delivered by cesarean section.

TABLE III

YEAR	TOTAL	BAG	CESAREAN SECTION	PER CENT BAG	PER CENT CESAREAN SECTION
1932	5	2	0	44.1	30.9
1933	12	8	1		
1934	15	6	5		
1935	19	8	8		
1936	17	6	7		
1937	17	4	10	26.8	53.6
1938	13	3	8		
1939	12	5	4		
1940	14	3	8		
1941	11	2	9	15.8	68.4
1942	14	1	11		
1943	7	3	3		
1944	6	0	3		
Total	162	51	77	31.5	47.5

Table IV shows the average length of time spent in the hospital following delivery. Slightly less time was spent in the hospital by the group delivered spontaneously than by those who had been treated with the hydrostatic bag. This is due largely to the fact that the multiparas in this group had a much shorter convalescence. The chart also shows that the length of the hospital stay averaged six days more following cesarean section than for any other type of delivery.

TABLE IV

	SPONTANEOUS		HYDROSTATIC BAG		CESAREAN SECTION	
	NUMBER OF CASES	AVERAGE STAY IN HOSPITAL	NUMBER OF CASES	AVERAGE STAY IN HOSPITAL	NUMBER OF CASES	AVERAGE STAY IN HOSPITAL
Primiparas	9	13.8	10	13.5	32	19.8
Multiparas	14	11.8	11	13.6	45	18.2
Total	23	12.6	51	13.6	77	18.9

In Table V the morbidity and average stay in the hospital for the various types of delivery is presented. Any patient having an elevation of temperature to 38° C. (100.4° F.) or over for any two days was considered to have morbidity. Any patient having an elevation in temperature to this level during labor was considered to have an intrapartum infection and even though there was no elevation in temperature following delivery, such a patient was classed as a morbidity. Using these criteria it is seen that there was a marked increase in the morbidity rate for the cesarean section group as might be expected for any laparotomy. The lowest morbidity rate was in those delivered spontaneously or by breech or forceps without prior use of the hydrostatic bag. In this group simple rupture of the membranes was sufficient to control the bleeding. Here the morbidity was 30.8 per cent as compared with a morbidity of over 50 per cent for the other types of vaginal delivery. The average stay in the hospital was 12.4 days, which is seen to be slightly less than for the other types of vaginal delivery.

TABLE V

Table VI presents a study of the fetal mortality for the various types of delivery. Since in some cases the choice of the type of delivery would be altered if there was no chance of obtaining a living infant, it was deemed advisable to correct the figures in order to get a better picture of the results. Therefore, in the corrected figures, where there was no fetal heart heard on admission, where the infant was under 1,500 grams, and where there was a monstrosity or other disease in the infant, such as erythroblastosis fetalis, these cases were excluded. There was little change in the gross and corrected fetal mortality rates in the groups in which the hydrostatic bag was used. In the group delivered by version and extraction alone there was a gross mortality rate of 57.1 per cent and a corrected rate of 0. Since there were only 7 cases in the group it is probably too small to be of any real significance. In the group of 26 cases which were delivered either spontaneously or by breech or forceps without the prior use of the Voorhees bag, there was a change from 34.6 per cent to 11.5 per cent from the gross to the corrected mortality rates. This latter figure is almost the same as that obtained in the group of 77 patients who were delivered by cesarean section.

TABLE VI

TYPE OF DELIVERY	NUMBER OF CASES	TOTAL FETAL MORTALITY			
		GROSS		CORRECTED	
		(NO.)	(%)	(NO.)	(%)
Bag with spontaneous breech or forceps	25	12	48.0	10	40.0
Bag with version and extraction	26	11	42.3	9	34.6
Version and extraction alone	7	4	57.1	0	00.0
Spontaneous breech or forceps	26	9	34.6	3	11.5
Cesarean section	77	14	18.2	9	11.7
Total	161	50	31.1	31	19.3

Table VII presents an analysis of the two types of cesarean section that were used and the two types of anesthesia. It should be noted that one case was delivered by radical section, hence the total of the classical plus the low flap cesarean groups is 76 and not 77. The variations in the fetal mortality, morbidity, and average stay in the hospital for the four groups are so slight that it would be difficult to prove that the type of section or anesthesia were of any real significance.

TABLE VII

	NUMBER OF CASES	FETAL MORTALITY				MORBIDITY		
		TOTAL		CORRECTED		NUMBER OF CASES	PER CENT	AVERAGE STAY IN HOSPITAL
		(NO.)	(%)	(NO.)	(%)			
Classical cesarean section	46	10	21.7	6	13.0	34	73.9	20.2
Low flap cesarean section	30	4	13.3	3	10.0	21	70.0	17.1
Cesarean section with general anesthesia	52	8	15.4	6	11.5	38	73.1	19.7
Cesarean section with local anesthesia	25	6	24.0	3	12.0	17	68.0	17.2
Totals	77	14	18.2	9	11.7	55	71.4	18.9

In Table VIII it is seen that treatment was delayed four or more days following admission in 63, or 56.8 per cent, of the service cases, while among the private patients only 12, or 23.5 per cent, were treated in this way. This delayed method was used in 75, or 46.3 per cent, of the total number of cases. The longest interval between entry to the hospital and delivery was sixty-two days.

TABLE VIII

	NUMBER OF CASES	DELIVERED FOLLOWING FOUR DAYS OR LONGER	
		(NUMBER)	(PER CENT)
Private	51	12	23.5
Service	111	63	56.8
Total	162	75	46.3

We believe that there are two advantages in delaying the treatment of placenta previa cases wherever it is possible. In the first place any operative procedure is less hazardous if one allows the patient to recover completely from the initial shock, however slight this may

TABLE IX

TYPE OF CASE	AGE	PARA	PERIOD OF GESTATION	CONDITION BEFORE TREATMENT	TREATMENT	TIME OF DEATH	COMPLICATIONS	REMARKS
Marginal	39	0	39	Excellent	Low flap cesarean section with general anesthesia. 500 c.c. transfusion postoperative	10th day	Febrile one day only. Pulmonary embolus	Pain and congestion in chest on 11th day with temperature 37.8° C. on 12th day
Central	29	ii	29	Excellent	Extraovular bag No. 3 four days before delivery. Braxton-Hicks version. Easy extraction	24th day	Pelvic thrombosis. Pulmonary embolus	Patient obese. Intrapartum infection. Afebrile puerperium. Discharged 12th day. Readmitted 17th day. Died 24th day
Partial	39	vi	33	Moderate shock	Intraovular bag No. 5. 500 c.c. transfusion	Undelivered	Temperature 39° C. on admission. Died 7 minutes after start of transfusion	May have been transfusion reaction
Marginal	32	iii	30	Slight painless bleeding. Dead fetus	Version and extraction. Manual removal of placenta. 1,000 c.c. transfusion	10th day	Macerated fetus 760 grams. Erythroblastosis. Patient Rh-. Donor's blood Rh+.	Hematin crystals demonstrated in kidney tubules at autopsy
Central	37	vii	39	Slight bleeding. Intrapartum infection. Temp. 38° C. Dead fetus	Version and extraction. Hysterectomy. 2,000 c.c. transfusion	7 hours post partum	Severe shock following delivery. Ruptured uterus	

be. Second, we believe that the chances of infection are diminished if this waiting period can be observed. It is therefore possible to have the advantages of an elective operation if cesarean section is decided upon.

There were 7 patients who developed phlebitic phenomena in the series, an incidence of 4.3 per cent. Five of these occurred following cesarean section, making an incidence of phlebitis of 6.5 per cent in this group. Three of the 7 patients had thrombophlebitis alone while the other 4 also had pulmonary emboli. Three of the cases were delivered by classical cesarean section and 2 by low flap cesarean section. One patient had local anesthesia and the other 4 had general anesthesia. Of the 2 patients who were delivered vaginally, one delivered by breech extraction following a Voorhees bag insertion and a Braxton-Hicks version; the other patient was delivered by craniotomy.

There were 5 maternal deaths in the series, making a mortality rate of 3.1 per cent. There was one death among the patients who were delivered by cesarean section, making a mortality rate of 1 to 77 cases, or 1.3 per cent. One patient died before delivery so that the death rate for the vaginal group was 3 in 84, or 3.6 per cent.

Table IX shows that two of the five deaths were due to pulmonary embolus. The first was a 29-year-old primipara with a marginal placenta previa who was delivered by a low flap cesarean section under general anesthesia. A 500 c.c. blood transfusion was given following operation. She died on the sixteenth day although she had been febrile only one day and had exhibited no symptoms of thrombophlebitis. The second patient had a central placenta previa. She was 29 years of age and had had two full-term pregnancies. She was delivered of a 1,510-gram stillborn infant by breech extraction following a Braxton-Hicks version. Four days before this a Voorhees bag had been inserted extraovularly. She had an intrapartum infection but the puerperium was afebrile and she was discharged from the hospital on the twelfth day. She was readmitted to the medical service on the seventeenth day with a diagnosis of pelvic thrombosis and pulmonary embolus. She died on the twenty-fourth day following delivery.

There were two deaths which occurred possibly as the result of a transfusion. One patient, who was 39 years of age and had had six full-term pregnancies, had a partial placenta previa at the time of insertion of a Voorhees bag intraovularly. She was in moderate shock, and a 500 c.c. transfusion was started at the end of the procedure. She died undelivered seven minutes after the start of the transfusion. There was no other obvious cause for her death. The other patient was 32 years of age and had had three viable infants. She was found to have a marginal placenta previa and was delivered of a 760-gram macerated fetus by version and extraction. The infant was later found to have erythroblastosis fetalis. Following delivery the mother was transfused for mild shock and died in anuria on the tenth day.

The last patient was 37 years old, para vii, with a central placenta previa. A version and extraction were performed, following which it was found that the uterus was ruptured. Immediate hysterectomy was performed and 2,000 c.c. of blood were given by transfusion. The patient succumbed to shock seven hours after delivery.

Summary

A study of 162 patients with placenta previa is presented. The delay in operative treatment for careful study of bleeding patients who probably have placenta previa is not only feasible, but wise. We have found an increase in the incidence of the use of cesarean section to be advantageous. The best results from vaginal delivery were obtained in those cases in which the bleeding could be controlled by simple rupture of the membranes and the fetus delivered either spontaneously, by forceps, or by breech extraction. However, each patient should be evaluated as to the method of delivery. While there was slight increase in the morbidity rate and an increase in the number of days the patient remained in the hospital following cesarean section, the fetal mortality was greatly improved and the delivery simplified by this procedure. The type of cesarean section and the choice of anesthesia seems to be of little importance. Further study toward prevention of phlebitis is important.

We wish to take this opportunity to thank Dr. Henricus J. Stender for the privilege of presenting this study.

Discussion

DR. BENJAMIN P. WATSON.—I personally have gone through the different phases in the treatment of this condition. In 1925, when I was in Edinburgh, Dr. Douglas Miller and I made a review of our cases of placenta previa and came to the very definite conclusion that there were only two ways of treating it: one, by doing nothing at all, or by simple rupture of the membranes in the marginal cases; and the other, by cesarean section in the cases of partial and central placenta previa where the patient was not in labor and where the cervix was firm and unretracted. Then I came to Sloane Hospital in 1926, the home of the Voorhees bag, and found that the bag treatment of placenta previa was the accepted method in the great majority of cases. I went along with that method, and for many years after I came here the Voorhees bag was used in most of our cases of placenta previa. Then last year we made a ten-year review of our cases of placenta previa which had been treated by simple rupture of the membranes, with the hydrostatic bag, and by cesarean section. From a review of that series we came to the same conclusions as those given us tonight, namely, that there are but two ways of treating the condition, simple rupture of the membranes or cesarean section.

I believe the hydrostatic bag belongs to a past era in obstetrics. It did a good job in the days when cesarean section was a hazardous operation, but I personally think that the Voorhees bag has a very limited place in the treatment of placenta previa in a modern obstetric service.

It might be of interest to mention the figures that we got in our ten-year study of placenta previa at the Sloane Hospital. We found, in contrasting cesarean section with bagging, in cases of central or of partial placenta previa, that the fetal mortality in our cesarean section cases was 4.1 per cent and in our bagging cases, 50 per cent; that the maternal mortality in cesarean section was 3.4 per cent and in bagging, 11.5 per cent; that the morbidity in bagging cases was 57.6 per cent and in cesarean section, 37.9 per cent; and as regards the patients who had lost a great deal of blood and were in profound shock, we found in cesarean section 16.3 per cent and in the bagging cases, 61.5 per cent. There was a lower fetal mortality, a lower maternal mortality, less shock, and less hemorrhage in the cesarean section cases than in those that had been bagged.

We also compared rupture of the membranes with bagging in cases of marginal placenta previa. These were the figures: the fetal mortality with simple rupture of the membranes was 16.6 per cent as against 25 per cent with bagging. We found that shock and hemorrhage occurred not at all in cases of simple rupture of the membranes, and that 62.5 per cent of the patients were shocked when bags were used.

So with these two comparisons of the severe types of placenta previa, bagging versus cesarean section, there was no question but that section had the better showing; and in the milder marginal placenta previa cases, rupture of the membranes versus bagging, simple rupture was superior.

DR. GEORGE H. RYDER.—To consider placenta previa as of one type only, is confusing and illogical, as the treatment and results vary so widely with the situation of the placenta, from the innocuous lateral type, through the dangerous marginal type, to the complete type—one of the most serious complications of pregnancy. Fortunately, over 60 per cent of previas are of the lateral type and probably not more than 6 per cent are of the complete type.

Dr. Watson has stated that there are only two methods of treating previas, rupturing of the membranes and section. This is practically true. But unless he explains that rupturing of the membranes is the treatment of lateral previa, and section of the complete, and serious forms of marginal previa, his statements will be misunderstood.

management decided on, I see no reason for not proceeding to carry it out at once. That is our practice.

Our actual incidence of section in these cases is almost exactly comparable to Dr. Williamson's in his last period of observation, namely, about 65 per cent.

DR. HARVEY B. MATTHEWS.—There are three points that I would like to touch upon.

First, I would like to disagree somewhat with Dr. Watson regarding the use of the Voorhees bag in the management of placenta previa. I agree that rupture of the membranes and cesarean section are the two outstanding methods of treatment. On the other hand, there are certain cases of marginal placenta previa in multiparous women, where rupture of the membranes does not completely control the bleeding, and in those cases we still use the bag successfully. On the other hand, it is true, as time goes on and as the technique of cesarean section has been greatly improved, that "bags" are dwindling in their popularity. However, I still think that there are a few selected cases in which the bag can be used very successfully.

The second point was more or less covered by Dr. Cosgrove and that is that we have always believed and taught that, when the diagnosis is made, there is no expectant treatment of placenta previa. Of course, there may be an occasional exception to this sweeping statement.

Third, I agree with Dr. Ryder that we should differentiate between marginal, lateral, and central placenta previa. As soon as this is done, there is no reason for delay in choosing the method of procedure. We proceed to make the diagnosis by repeated cystograms. One cystogram, if positive, may be sufficient; but, if negative, it is not very helpful. Therefore we may do one, two, three, or more cystograms, if conditions warrant. Then, under proper surroundings, as has already been outlined, we do a vaginal examination in order to determine further the type of previa we are dealing with. Following these procedures, that is, having made the diagnosis of placenta previa and determined the type, the appropriate treatment is instituted. This may be simple rupture of the membranes, insertion of Voorhees' bag with or without vaginal pack, or cesarean section.

DR. RALPH L. BARRETT.—Time of treatment of the patient with premature separation of the placenta is of extreme importance.

If you see a patient for the first time late in labor with a partial dilation and an obliterated cervix, particularly in the multiparous patient, you may be able to handle the case successfully by delivery through the vaginal route. However, if the diagnosis is made early in labor or before labor and the cervix is not dilated and obliterated, I do not see how, in view of all that we have heard here tonight, that there can be the slightest question as to the proper method of treatment of placenta previa.

In my opinion, the proper method of treatment is delivery by the abdominal route when the patient is seen early and before the cervix has dilated and effaced with its incident hemorrhage.

DR. CLAUDE E. HEATON.—In 1934, Dr. J. P. Marr made a study of 146 cases of placenta previa treated at the New York Nursery and Child's Hospital, in which he came to practically the same conclusions we have had presented. Maternal mortality in delivery by the vaginal route was 5.6 per cent; in 40 cases treated by cesarean section the mortality was 2.5 per cent. The one death was due to transfusion reaction. The fetal mortality was 20 per cent in cesarean section and 49 per cent in vaginal delivery.

The mortality rate was just as high in those cases in which the placenta was situated in the least malignant situation as it was when the placenta was situated in the supposedly malignant site, centralis. In placenta previa the placenta is located in the lower uterine segment and death occurs from injury to this segment. Cesarean section is the operation of choice if one wishes to lessen the hazard for both mother and baby.

DR. ELIOT BISHOP.—The position of the placenta when implanted in the lower uterine segment should be considered from two points of view, the placenta and the cervical canal. At the risk of seeming to be too academic, I will give what I consider the proper nomenclature for each point of view. The placenta may be placed either centrally, laterally, or marginally, in relation to the cervical canal. From the point of view of the cervical canal the placenta previa may be either complete or partial. Examination usually shows only this viewpoint and not the placenta. I doubt that an x-ray cystogram will give us the differential.

Some deviations may occur from these academic viewpoints and nomenclature, such as velamentous insertion of the cord.

As to the treatment of placenta previa as such, I believe that everyone is in accord as to the proper planning and setup before even the examination is made. In the case of a primipara I will subscribe to the modern trend of using a cesarean section. If the patient is a multipara with living children, I think we cannot entirely discard the more conservative methods of vaginal attack. As the speaker and the previous discussers have stated, when the margin of the placenta is found, a simple rupture of the membranes will suffice. If it can be demonstrated that the placenta is presenting laterally and the cervix soft and dilated or easily dilatable, the Braxton-Hicks maneuver should be done.

However, this I do emphatically emphasize—after the foot is brought down there should *never* be *extraction*. A spontaneous delivery is obligatory. If we are committed to this procedure, the mother's and the child's life is our objective.

DR. GEORGE L. BOWEN.—In a study of placenta previa at Bellevue Hospital in 1938, Dr. Salter found that from 1922 to 1932, only 21 per cent of the patients with placenta previa received blood transfusions, and from 1932 to 1938, 50 per cent received them. This resulted in a decrease in the mortality from 11.5 per cent to 2.0 per cent. As Dr. Greeley has emphasized, there are other factors than just the method of delivery which have contributed to the lowering of the mortality rate.

DR. ARTHUR V. GREELEY (closing).—In answer to Dr. Cosgrove: it is difficult to prove the value of this waiting period. However, we feel that these patients are in better condition to withstand operative intervention at this time than they are at the time of admission when they have not recovered from the effects of the initial hemorrhage. We believe that our results were partly due to observing this waiting period.

SHOULD WE CHANGE OUR PRESENT STANDARD ON INFANT VIABILITY?

R. L. HAAS, M.D., ANN ARBOR, MICH.

(From the Department of Obstetrics and Gynecology, University of Michigan Hospital)

THE birth of a premature infant invariably arouses interest and invites speculation as to what constitutes the lower limit of viability. Periodically, one encounters newspaper articles giving the impression that the particular infant reported is the smallest on record. In order to discover the smallest authentically recorded premature baby, and at the same time re-evaluate our concept of the lower limits of viability, the literature on the subject has been carefully reviewed, and three cases of very premature infants from our own hospital are here recorded. The subject should be of special interest to those doing obstetrics, since upon the accoucheur commonly falls the responsibility for the immediate postnatal care so all-important for the survival of these tiny infants.

Various criteria are used to determine whether a fetus is viable. Thus, on the basis of the duration of pregnancy, a fetus which has remained in utero twenty-six to twenty-eight weeks is generally said to be viable.¹¹⁻¹² In terms of body length, this corresponds to about 35 or 36 centimeters.¹⁴ Still another standard is that set by law, which varies among the states but usually requires birth and death certificates for an infant when the duration of gestation is five months or more (Table I). This is in accord with the Model Vital Statistics Act of 1941. However, sixteen states and the District of Columbia have other legal limits, varying from that of Maryland (any recognizable product of conception) to those of Washington and Indiana (seven months or over). A point which should be obvious, yet bears

TABLE I. PERIOD OF GESTATION AT WHICH REPORTING OF STILLBIRTHS IS REQUIRED

STATE	MINIMUM PERIOD OF GESTATION
	<i>Agrees With Model Vital Statistics Act, 1941</i>
Alabama	Advanced to 5th month
Arizona	Advanced to 5th month
Arkansas	5th month
California	Advanced to 5th month
Colorado	5 months (20 weeks) or more
Delaware	5 months
Florida	Advanced to 5th month
Georgia	Advanced to 5th month
Illinois	Advanced to 5th month
Iowa	Advanced to 5th month
Kansas	Passed 20th week
Louisiana	5 months (20 weeks) or more
Maine	5 months or more
Michigan	Advanced to 5th month
Minnesota	Advanced to 5th month
Mississippi	5 months
Missouri	5 months
Nebraska	Advanced to 5th month
Nevada	After at least 20 weeks
North Carolina	Advanced to 5th month
North Dakota	5 months
Oklahoma	Advanced to 5th month
Oregon	After at least 20 weeks
South Dakota	Advanced to 5th month
Tennessee	5 or more months
Texas	Advanced to 5th month
Utah	Advanced to 5th month
Vermont	5 months or over
Virginia	5 months (20 weeks) or more
West Virginia	Advanced to 5th month
Wisconsin	5th month
Wyoming	After at least 20 weeks
	<i>Less Than 20 Weeks</i>
Maryland	Any recognizable product
New York*	New York City—every product of conception
Ohio	At least 4½ months
Pennsylvania	4 months
	<i>More Than 20 Weeks</i>
Connecticut	After not less than 28 weeks
District of Columbia	Passed 5th month
Idaho	Development sufficient to give chance of life
Indiana	7 months and over
Kentucky	5½ months
Massachusetts	After 5 months
Montana	6 months or 24 weeks
New Hampshire	28 weeks
New Jersey	Advanced beyond 5th month
New Mexico	5½ months
Rhode Island	6 completed months
South Carolina	22 weeks
Washington	Advanced beyond 7th month

*The law for New York State (exclusive of New York City) is in accord with the Model Vital Statistics Act.

emphasis, is that such criteria do not make survival impossible for infants who fail to measure up to them. Every effort should be made to save even those babies which appear nonviable by these standards.

It is accepted that the prognosis for survival of an infant varies with its weight. Those weighing less than 1,000 grams (2 pounds, 3 ounces) naturally do not have a very good outlook, yet a survey of the literature (Table II) shows that at least 54 such cases are on record. It is interesting to note that the smallest surviving infant had a minimum recorded weight of 420 grams (Monroe).

In 1941 two infants with minimum weights of less than 1,000 grams were born in the Maternity Division of the University of Michigan Hospital. Both were born of mothers with chronic nephritis. The pregnancies were interrupted artificially at about 6 to 6½ months of gestation, and the deliveries were spontaneous. The smaller infant weighed 705 grams (1 pound, 9 ounces) and the other 934 grams (2 pounds, 1 ounce) when first weighed on their

TABLE II. REPORTED CASES OF SURVIVING INFANTS WEIGHING LESS THAN 1,000 GRAMS

YEAR OF REPORT	REPORTED BY	MINIMUM WEIGHT RECORDED (GRAMS)	BIRTH WEIGHT	SEX
1922	Huber, O.	790		F
	Oberwarth	1921	500	
	Hess	1911	690	
	Hess	1911	740	
	Oberwarth	1911	750	
	d'Outrepont		750	
	Meyer	1912	750	
	Roth	1913	750	
	Heller	1912	800	
	Heller	1912	810	
	Ylppo		840	
	Frankenthal		850	
	Pfannndler	1907	860	
1922	Wuegele	1917	860	
Hess	Klinker	1903	895	
Collection	Ahlfeld	1903	900	
	Pizzini	1908	900	
	Jardine	1902	907	
	Villemain	1895	950	
	Maygrier and Schwab	1907	970	
	Heiberg		975	
	Rommel		980	
	Ahlfeld	1903	980	
	Tissier	1912	990	
1928	Pulford & Blevins		680	F
1930	Schoedel	720	800	M
		960	1,000	F
			950	M
			970	F
		980		F
1931	Fischer-Ban	510	600	
1931	Temesnary	600		
1933	Houlihan	666	705	M
		745	900	F
		840		F
		850	940	M
1934	Kunstadter and Bartelme	850	890	F
		905	995	F
		850		F
		940		M
		865		M
		890		F
		790		F
		970		F
		755	825	M
		890	1,005	M
		945	1,075	F
		970	1,075	F
		990	1,075	F
		945	1,060	F
		925	1,050	F
1936	Stander		928	
1938	Hoffman, Greenhill & Lundeen	595	735	F
1939	Monro	420		M
1945	Haas (present article)	705		M
		830		M
		934		M

ninth and sixteenth days, respectively. Both babies were cared for by the regular nursing staff, and were kept in incubators with continuous oxygen for nearly two months. Inhalations of 5 per cent carbon dioxide were used frequently during the first few weeks.

The third infant, born in 1944, weighed 830 grams (1 pound, 13 ounces) when first weighed, 16 days after birth. The circumstances surrounding the birth of this child were somewhat different than for the two preceding cases. The mother had intermittently threatened to abort from the third month until the sixth, when the membranes ruptured spon-

taneously, and labor ensued two weeks later. The baby was born spontaneously as a frank breech presentation. The placenta was incarcerated and required manual removal.

The care of all three infants was essentially the same. For several hours after birth nothing was given by mouth, and great care was taken to see that aspirated mucus and amniotic fluid were suctioned off as necessary. When respirations were well established (18 hours in the first two, and 48 hours in the last case), feedings of 5 per cent glucose water were offered in $\frac{1}{4}$ ounce quantities every two hours until it was well taken, at which time a formula was substituted.

In the absence of available breast milk, feedings consisted of an evaporated milk, corn syrup, and water formula. This was at first quite dilute, but was rapidly concentrated to give about 20 calories per ounce of formula. Occasionally, protein milk was added to increase the caloric value. The amount of each feeding was determined by the infant's appetite, starting with $\frac{1}{4}$ ounce and increasing as tolerated. It was interesting to note that under this plan the infants took enough formula to provide 65 to 80 calories per pound of body weight per day, this figure dropping gradually as the weight increased.

The sucking reflex was fairly well developed in all these babies. They were fed at first by means of a medicine dropper with a short piece of rubber tubing over the end for a mouthpiece. This was followed as tolerated by a Breck feeder, and finally by a regular nursing bottle. It should be emphasized here that the first feedings with the Breck feeder should be given by a nurse experienced in feeding babies. Otherwise, aspiration of formula with disastrous results is likely to occur. The administration of vitamins A, C, and D, and iron (elixir of ferrous sulfate) was begun in all cases as soon as the formula was being well taken. At no time was it necessary to resort to tube feeding. Subcutaneous fluids were used only rarely. Because of the infant's susceptibility to infection, and because of the greater amount of handling required, it is our policy to avoid the use of parenteral fluids whenever possible.

Follow-up has been obtained in each of the earlier cases. The smaller infant (J. M., No. 492130) is now over 3 years old. He stood alone at 18 months and began walking at 23 months. When 2 years old he had 16 teeth and weighed 24 pounds. His mother reports that he is the most active of her five children, eats anything offered, and has had no illnesses except a slight cold when about 14 months old.

The second child (G. F., No. 496857) has not been so fortunate. At the age of 6 months he was returned to the hospital as a feeding problem with rumination. It was also found that he had thrush, ocular nystagmus, and retinal hemorrhages. It was felt that the prognosis for good vision was very poor. Under management by members of the Pediatrics Department the feeding problem was readily corrected, and on subsequent checkup at the age of 9 months he seemed to be progressing satisfactorily. It is now reported that he weighed 18 pounds at 1 year, and at 23 months weighed 25 pounds. He started to crawl at 13 months and took his first steps at 19 months. Sixteen teeth have erupted. His mother reports that she thinks vision of the left eye is poor but is "real good" in the other eye. He speaks several words, and seems very active and healthy now.

The third infant weighed over 6 pounds when discharged from the Hospital at a little over 3 months of age.

While excessive handling and unnecessary weighing are to be scrupulously avoided in caring for premature infants, the frequently reported *birth* weights of prematures indicates that curiosity often overbalances judgment. The infant should be placed in an incubator at once and the first weighing delayed until his condition warrants, whether this be one or several weeks later.

One often encounters the contention that the prospects for satisfactory mental and physical development of very small premature infants do not justify the prolonged and tedious care which they require. This problem has received considerable attention and study, and it has been quite definitely shown by Hess, Mohr, and Bartelme⁸ that, excluding cases with birth injuries, premature infants show development comparable to that of normal children. Physical growth in early years tends to lag somewhat behind that of term infants. Hess¹⁰ reports similar findings.

The economic phase of this problem should also be considered. The great amount of special care and equipment necessary to raise a premature infant generally involves considerable expense. Again, the question may be asked, are

they worth it? If we use for comparison the care of patients afflicted with tuberculosis or malignant disease in which the outlook is often poor indeed, then the answer must be in the affirmative.

When hospitals can be equipped and staffed as we now feel they should be, the care of prematures will become more routine and less formidable, although some degree of special care and individualization will always be required.

In recent years certain developments have appeared which may be expected to improve the survival chances for premature infants. Among these may be mentioned new and improved incubators and other nursery equipment, which are becoming more readily available to all who need them; caudal anesthesia, which avoids excessive sedation and minimizes trauma to the delicate fetal head by relaxing the structures about the birth canal; and the Rh factor, knowledge of which may save many premature infants with hemolytic anemia of the newborn, through the use of proper transfusions. As a result of these advancements, it is likely that the number of prematures born alive will rise, thus increasing the importance of the question under discussion.

Discussion

To designate a given weight as the lower limit of viability can have no particular virtue except for statistical purposes. It can, however, engender the attitude and belief that no infant weighing less than such a standard can survive and therefore does not merit detailed attention. It is clear that although a given viability standard may be important to the public health statistician, it may actually be a handicap to the physician. Because of this and the evidence presented, it is obvious that the advantages are all in having the limit too low rather than too high. If there must be a standard, let it be based on recorded survivals. It is suggested that 1,000 grams (2 pounds, 3 ounces) would be a reasonable weight limit.

The number of recorded infants weighing less than 1,000 grams who have survived is not great, yet there are enough to show that every infant, no matter how premature, deserves full attention and opportunity for life. Some will survive, and most of the survivals will develop into worth-while individuals.

Summary

1. The literature on the survival of premature infants with minimum weights of less than 1,000 grams has been reviewed and 54 cases found.
2. Three additional cases are reported.
3. Some recent developments which improve the survival rate for premature infants have been mentioned.
4. In the absence of available breast milk, properly adjusted artificial formula feedings have been found a satisfactory substitute.
5. It is pointed out that with increasing awareness of the possibilities of survival, and with greater effort, infants previously considered nonviable will survive.
6. One thousand grams (2 pounds, 3 ounces) is proposed as a lower weight limit of viability for statistical purposes.

References

1. Pulford, D. S., and Blevins, W. J.: *Am. J. Dis. Child.* 36: 797, 1928.
2. Schoedel, J.: *Jahrb. f. Kinderh.* 129: 143, 1930.
3. Temesvary, R.: *Zentralbl. f. Gynäk.* 55: 1319, 1931.
4. Fischer, H.: *Klin. Wchnschr.* 10: 1354, 1931.

5. Houlihan, J. D.: Practitioner 130: 608, 1933.
6. Hoffman, S. J., Greenhill, J. P., and Lundeen, E. C.: J. A. M. A. 110: 283, 1938.
7. Monro, J. S.: Canad. M. A. J. 40: 69, 1939.
8. Hess, J. H., Mohr, G. J., and Bartelme, P. F.: The Physical and Mental Growth of Prematurely Born Children, Chicago, 1934, University of Chicago Press.
9. Othmar, Huber: Cited by Kunstadter and Bartelme.
10. Hess, Julius H.: Premature and Congenitally Diseased Infants, Philadelphia, 1922, Lea & Febiger.
11. Stander, H. J.: Williams' Obstetrics, ed. 8, New York, 1936, D. Appleton-Century Co.
12. DeLee, J. B., Greenhill, J. B.: Principles of Obstetrics, Philadelphia, 1943, W. B. Saunders Co.
13. Schumann, E.: Textbook of Obstetrics, Philadelphia, 1936, W. B. Saunders Co.
14. Boyd, Edith: Outline of Physical Growth and Development, Minneapolis, 1941, Burgess Publishing Co.
15. Stillbirth and Maternal Mortality Rates: Am. J. Pub. Health 34: 889, 1944.

THE TREATMENT OF PRIMARY DYSMENORRHEA WITH DEPROTEINATED PANCREATIC EXTRACT (DEPROPANEX*)

LAWRENCE L. GROSSMANN, M.D., MILWAUKEE, WIS.

DYSMENORRHEA has been classified arbitrarily in two categories, primary and secondary. The latter usually appears during the third decade of life or later, and, in the majority of patients, fairly well defined pelvic pathology can be demonstrated. Careful study will usually reveal the presence of ovarian or uterine neoplasm, oophoritis, salpingitis, endometriosis, or some other tangible clinical entity which can be treated with directness and frequently with success. Primary dysmenorrhea, to which this discussion will be confined, commonly appears at or shortly after the menarche and is encountered, therefore, in young women who are usually nulliparous or virginal. Childbearing, although apparently helpful in many instances, will not guarantee complete or even partial relief from dysmenorrhea after the postpartum period. Menstruation usually occurs at regular intervals in these young women and the rate and amount of flow approximate the normal. Pelvic structure is within the normal range and, as a general rule, no pathologic conditions are demonstrable.

The treatment of primary or functional or essential dysmenorrhea has been most unsatisfactory for both clinician and patient because the etiology of the condition as yet is unknown. Many theories have been advanced and as many methods of treatment have been developed.

One of the oldest theories suggested that dysmenorrhea occurred in those individuals with certain structural defects such as stenosis of the cervix, anteversion or retroversion of the uterus, complete or partial infantilism of the genital tract, and a variety of other defects of greater or less importance. Corrective measures sometimes afford permanent or temporary relief, but since such procedures require a considerable degree of patient-physician cooperation or demand surgical intervention, they are not practicable under all circumstances. Furthermore, it is now rather widely accepted that the incidence and severity of structural defects are no greater in women who suffer with dysmenorrhea than in those who are not so afflicted.

*Depropanex is the proprietary name of deproteinated pancreatic extract prepared by Sharp & Dohme, Philadelphia, Pa.

Some aberration of the pelvic autonomic nervous system is sometimes thought to be responsible for the collective phenomena of dysmenorrhea. Attempted correction of such aberration is usually reserved for extreme cases and as a last resort. Even when careful technique is employed, however, surgical intervention is by no means always successful.

It is held by some that psychogenic factors are of major importance in women with dysmenorrhea. This is undoubtedly true in certain instances but by far the majority of dysmenorrheic women are emotionally stable and reveal no greater tendency toward neuroses or psychoses than do other individuals. It is also entirely possible that dysmenorrhea might precipitate or exaggerate a psychopathologic personality rather than the reverse.

During the past few years, a number of endocrine substances have been employed in an attempt to relieve or eliminate dysmenorrhea. Estrogens have little or no effect according to Winther,¹ but the results of other investigators^{2,3} indicate that these substances are capable of affording relief. Prolonged administration of the estrogens is necessary and the desired effect is attained by the induction of an anovulatory cycle. Lyon⁴ has had favorable results with ethinyl estradiol, but oral medication must begin on the fifth day of the cycle and continue for twenty-one days. Relief from dysmenorrhea is afforded by the prevention of ovulation, which may not be desirable even temporarily in many instances, and certainly, as Lyon⁴ states, "prolonged ovarian rest or follicle-stimulating hormone suppression has not been shown to be desirable." Laboratory and clinical evaluation have failed to produce evidence in favor of progesterone.⁵⁻⁷ Androgens have also been used in an effort to reduce uterine bleeding or rather to "prevent relative pelvic vascular engorgement with its attendant effects on the pelvic sympathetic nervous system."⁸ When androgens are employed, care must be taken to avoid possible atrophy of the endometrium which, of course, is most undesirable in women of the age-group in which primary dysmenorrhea occurs. Atrophy can probably be avoided by administering the small doses recommended by Cinberg,⁸ but frequent subcutaneous injections are necessitated by such a procedure which greatly restricts its applicability.

Billig⁹ has introduced a new method recently for relief from dysmenorrhea which is based upon the premise that in dysmenorrheic women "a postural defect of contracted ligamentous bands restricting the normal range of spinal-pelvic-femoral postural excursion is found present." The ligamentous contractures cause compression of nerve pathways which produces irritation to certain peripheral nerves. "This irritation gives rise to painful symptoms in the region of the distribution of these nerves and is proposed as the mechanics involved in producing symptoms of dysmenorrhea." Specific exercises are recommended for correction of this condition. The exercises are to be practiced three times daily and it is claimed that relief is afforded in from one to three months. Close supervision is required in order to direct proper execution of the special exercises. Such a regimen does not appear practicable for industry nor for many patients encountered in general practice, although good results are claimed by Dick, Billig, and Macy.¹⁰

Bickers¹¹ confirmed the work of Wilson and Kurzrok¹² on the normal human uterus, and later¹³ demonstrated the difference between the painful and nonpainful menstruating uterus by kymographic tracings of uterine contractions prior to and during menstruation. Bickers believes that there is a congenital physiologic defect in the myometrium causing the latter to react abnormally to the stimulus, which induces increased motility at the beginning of menstruation. The muscle is thrown into spasm and fails to relax between contractions. The absence of relaxation between contractions produces fatigue and "interferes with the normal oxygenation and nutrition of the myometrium. Muscle contraction in the presence of anoxia is associated with pain,"¹² and the symptoms of dysmenorrhea result. Bickers observed the effects of a number of drugs and endocrine substances when administered to normal and dysmenorrheic patients, but none were shown to have any favorable effect on uterine contractions with the exception of a nonnarcotic spasmolytic compound. It is interesting to note that this compound has papaverine-like properties and exerts its activity directly on the smooth muscle fiber itself. Unfortunately, the favorable effect of this drug was noted in only about one-third of patients when administered orally.

In a review of the literature concerned with essential dysmenorrhea Fremont-Smith¹⁴ concludes that "the pain of dysmenorrhea does not occur in the absence of active uterine

contractions; and one or more secondary factors must be present if pain is to occur. If this is true, treatment of the disorder could be effective either by causing diminution of uterine contraction or by influencing this unknown secondary factor. One may regard the contraction as the precipitating and some other endocrine or circulatory factor as the predisposing cause of dysmenorrhea."

With these facts in mind and with some experience in the use of most of the methods presently discussed, an attempt was made to discover a preparation which was nontoxic, which would produce the desired effect rapidly and with reasonable certainty in the majority of patients. The conclusion of Fremont-Smith appeared reasonable, and since the secondary factor was not known, a search was made for a substance which would diminish the contractions of the menstruating uterus. A review of the literature revealed that a suitable preparation was available which had an extensive clinical background but was employed almost exclusively in the fields of peripheral vascular disease¹⁵⁻²⁰ and in urology.²¹⁻²⁴ These reports indicate that the preparation is nontoxic and that it affects a relaxation of spastic smooth muscle.

Depropanex is a saline solution of a chemically derived, protein-free nitrogenous fraction obtained from an acid-alcohol treatment of beef pancreas. It is free of insulin, histamine, and acetylcholine, and contains approximately 2.5 per cent solids, including 0.5 per cent nonprotein nitrogen, 0.9 per cent sodium chloride, and 0.25 per cent phenol, as a preservative. The pH of the solution is adjusted to 6.5—6.8. The dose recommended in the current literature which describes clinical experience with this pancreatic tissue extract is from 2 to 5 c.c., administered intramuscularly.

Inasmuch as the stimulus for such an investigation emanated in part from a desire to reduce absenteeism in the industrial plants with which the author was associated on a part-time basis, it was decided to conduct this study in two plants, the personnel of which included a large number of women. The nurses at each of these plants were instructed, therefore, to administer depropanex intramuscularly to all employees who presented themselves for relief of dysmenorrhea. Since there was little or no information with regard to dosage in the treatment of this condition, it was considered advisable to begin with less than the minimal dose recommended for the more serious circulatory and urologic disorders described in the literature. Standing orders were written for 1.5 c.c. of depropanex to be administered intramuscularly. After the injection, provision was made for the patient to rest for a short period before returning to work or, if relief was not obtained, to be discharged to her home with the usual recommendations for palliative treatment. The same regimen was adopted for those patients seen in private practice. In some instances the dose was increased up to 4 c.c., but for the majority of patients 1.5 c.c. of the extract appeared to be sufficient.

It soon became evident that a number of factors were to be considered in the industrial study which did not appear in the investigation as conducted among private patients. There was a large labor turnover in the industrial plants and consequently it was frequently impossible to do follow-up studies or to repeat the medication in larger doses. Some employees, having been accustomed to oral medication and in many instances fully expecting to be excused from work because of the severity or alleged severity of symptoms, resisted parenteral treatment. It is interesting to note that in both plants when the pancreatic tissue extract was first used the majority of employees to whom

it was administered voluntarily extended favorable comments. These subjective observations were borne out by improved clinical appearance and the ability of the patient to return to work. Later, however, a number of vague and indefinite objections were raised in order to avoid the administration of the preparation. In a few instances in which such remonstrance was assuaged by the nurses, the patients denied any beneficial effect after the extract was administered. In most cases, however, such denial was not substantiated by the clinical appearance, since the general tension and the characteristic appearance of the facies had subsided markedly or had disappeared completely. Inasmuch as the symptoms of dysmenorrhea are almost entirely subjective, however, these employees were permitted to leave the plant, ostensibly to seek relief at home.

The experience among patients treated in private practice was quite different, and definite uniformly successful results were obtained in almost every instance. The degree of relief varied somewhat in different individuals, but in no case did the patient state that no relief whatever had been obtained after administration of the extract. It must be admitted, of course, that the patients seen in private practice were studied much more carefully than those in industry and that there was no doubt that the patients in the former category were properly classified with regard to the type of dysmenorrhea with which they were suffering, i.e., primary or essential dysmenorrhea. The majority of patients seen in private practice and included in this series had received a variety of therapeutic agents, including parenteral injections for relief from the symptoms of dysmenorrhea. Although some of these agents had afforded sufficient relief for the patient to resume her usual activity, none produced so marked an effect with such consistency as did pancreatic tissue extract. Relief in some instances has been so marked and has occurred with such relative rapidity that the patients so affected felt that a narcotic had been employed except for the fact that they experienced no drowsiness or other side effects which commonly result from such treatment. A noticeable decrease in pain occurs in most instances within fifteen minutes after administration of depropanex. In some patients the pain has almost completely disappeared within this time. In other individuals relief is more gradual and thirty minutes to one hour is required for amelioration or disappearance of symptoms. A few patients have noted that after several treatments the symptoms of dysmenorrhea have diminished to such an extent or have disappeared entirely so that further treatment has become unnecessary.

The history of one patient, perhaps, deserves special mention. She was 20 years of age and had had severe dysmenorrhea since the onset of the menarche at 14 years of age. She was unmarried, had had no pregnancies, and had been incapacitated for from one to three days consistently throughout her menstrual life. Hospitalization and thorough study on several occasions have failed to elicit any tangible cause for dysmenorrhea of such severe type. Depropanex was administered on two occasions in amounts of 2 and 4 c.c., respectively, with no favorable results. During the course of the next month a presacral neurectomy was performed and the subsequent menstrual period, which occurred shortly after partial recovery from the operative procedure, was quite painful and no improvement was noted as compared with the dysmenorrhea experienced before operation. After the pain had continued with no evidence of abatement for four hours, 2 c.c. of depropanex were administered intramuscularly. Partial relief was obtained in fifteen minutes and almost complete relief within one hour. The same experience was observed on three subsequent occasions. At this writing it appears that the symptoms are gradually diminishing in severity. During the last menstrual period no medication was administered and, although

moderate pain was experienced, the patient was by no means totally incapacitated as previously.

Table I shows the number of patients in each group, the number of treatments administered, and the number and percentage of treatments which resulted in complete and partial relief or in which no relief was obtained. Included in the latter group are those patients treated in industry who denied favorable response but whose clinical appearance, according to the observation of the attending nurse, was definitely improved. The marked disparity between the results obtained in industry and those obtained in patients encountered in private practice is most striking. In addition to the reasons outlined above which contributed to this wide difference, it is believed that closer medical supervision, such as that which can be maintained by a full-time industrial physician, would probably result in more favorable response to this method of treatment in industry and it would be possible to approximate the results obtained in private practice.

TABLE I. SHOWING THE NUMBER OF PATIENTS IN EACH GROUP, THE NUMBER OF TREATMENTS, AND THE NUMBER AND PER CENT OF RESULTS OBSERVED

CLASSIFICATION OF PATIENTS	NUMBER OF PA- TIENTS	NUMBER OF TREAT- MENTS	CLINICAL RESULTS					
			COMPLETE RELIEF		PARTIAL RELIEF		NO RELIEF	
			NO.	%	NO.	%	NO.	%
Private	25	63	50	79.4	11	17.5	2*	3.1
Indus- trial	31	41	22	53.7	6	14.6	13	31.7
Total	56	104	72	69.3	17	16.3	15	14.4

*These treatments were those administered to Miss G. W., whose case history is outlined above, prior to operative intervention.

No attempt was made during the course of this investigation to extend additional contributions concerning the etiology of primary dysmenorrhea. On the basis of the already accumulated knowledge, which is admittedly incomplete, an attempt was made to discover some preparation capable of producing a satisfactory clinical result. The favorable results obtained in this study and, particularly, the consistent success attained in a group of patients under close supervision indicate that the nontoxic, spasmolytic pancreatic tissue extract, depropanex, is a most valuable agent for relief of patients with dysmenorrhea and merits the attention of the profession for more extensive clinical evaluation.

Summary and Conclusions

1. A review of the literature reveals that no therapeutic agent has been available to the clinician which will afford consistently favorable results in the treatment of dysmenorrhea.

2. Recent laboratory and clinical investigation have clarified, to some extent, some of the factors involved in the production of dysmenorrhea and have indicated that the latter occurs only in the presence of active uterine contractions and that these contractions are spastic in character.

3. The effect of a nontoxic, spasmolytic agent, depropanex, which is a deproteinated pancreatic extract, was studied when administered to two groups of patients.

4. Uniformly consistent and favorable results were observed in the group of patients encountered in private practice who presented themselves for treatment for moderately severe, and severe dysmenorrhea. Twenty-five patients in this group received sixty-three treatments consisting of from 1.5 c.c. to 4 c.c.

of depropanex intramuscularly. Complete relief from dysmenorrhea was afforded within from fifteen minutes to one hour subsequent to the administration of fifty treatments (79.4 per cent). Partial relief was afforded within the same period of time after eleven treatments (17.5 per cent). Complete or partial relief, therefore, was obtained in twenty-five patients on sixty-one occasions which represent 96.9 per cent of treatments administered to this group.

5. Thirty-one patients included in the industrial group received forty-one treatments, twenty-two, or 53.7 per cent, of which afforded complete relief, and six, or 14.6 per cent, afforded partial relief from dysmenorrhea. Favorable response was denied after thirteen treatments (31.7 per cent).

6. The striking disparity of results obtained in the two groups are reasonably accounted for, and it is believed that if the factors mentioned were corrected, the experience in the industrial group would approximate that attained in the series of patients over whom closer supervision was maintained.

7. The results of this investigation indicate that deproteinated pancreatic extract is very effective when administered to patients with dysmenorrhea, and that favorable response is probably due to the spasmolytic action of depropanex on the uterine muscle.

Acknowledgment and deep appreciation are accorded Miss Genevieve Guilfoile, R.N., Miss Mildred Shier, R.N., and Mrs. Doris Berghold, R.N., for their cooperation and assistance during the conduct of this study.

References

1. Winther, N.: *Journal-Lancet* 62: 427, 1942.
2. Freed, S. C.: *Am. J. M. Sc.* 205: 735, 1943.
3. Sturgis, S. H., and Meigs, J. V.: *Surg., Gynec. & Obst.* 75: 87, 1942.
4. Lyon, R. A.: *Surg., Gynec. & Obst.* 77: 657, 1943.
5. Henry, J. S., and Browne, J. S. L.: *AM. J. OBST. & GYNEC.* 45: 927, 1943.
6. Kennard, J. H.: *Am. J. Physiol.* 118: 190, 1937.
7. Bickers, W.: *AM. J. OBST. & GYNEC.* 43: 663, 1912.
8. Cinberg, B. L.: *New York State J. Med.* 42: 2138, 1942.
9. Billig, H. E.: *Arch. Surg.* 46: 611, 1943.
10. Dick, A. C., Billig, H. E., and Macy, H. N.: *Indust. Med.* 12: 588, 1943.
11. Bickers, W., and Main, R. J.: *J. Clin. Endocrinol.* 1: 12, 992, 1941.
12. Wilson, L., and Kurzrok, R.: *Endocrinology* 23: 79, 1938.
13. Bickers, W.: *South. M. J.* 36: 192, 1943.
14. Fremont-Smith, M.: *New England J. Med.* 226: 795, 1942.
15. Fisher, M. M., Duryee, A. W., and Wright, I. S.: *Am. Heart J.* 18: 425, 1939.
16. Schwartz, M. S., et al.: *Am. Heart J.* 22: 122, 1941.
17. Wright, I.: *Arch. Surg.* 40: 163, 1940.
18. Fatherree, T. J., and Hurst, C.: *Northwest Med.* 39: 283, 1940.
19. King, G. S.: *Indust. Med.* 10: 530, 1941.
20. Klein, C., Saland, G., and Zurrow, H.: *Ann. Int. Med.* 18: 214, 1943.
21. Dodson, A. I.: *Synopsis of Genitourinary Diseases*, ed. 3, St. Louis, 1941, The C. V. Mosby Co.
22. Carroll, C., and Zingale, F. G.: *South. M. J.* 31: 233, 1938.
23. Walther, H. W. E., and Willoughby, R. M.: *New Orleans M. & S. J.* 95: 182, 1942.
24. Carroll, G.: *M. Clin. North America* 26: 343, 1942.

DIETHYLSTILBESTROL IN THE TREATMENT OF FUNCTIONAL OVARIAN DISORDERS

CAPTAIN GEORGE D. PATTON, MEDICAL CORPS, UNITED STATES ARMY

IT HAS been customary to consider the various functional disorders of the human ovary as distinct clinical entities. There are many articles in the literature on the causes, associated symptoms, and treatment of amenorrhea; other articles on menorrhagia; and others on hypomenorrhea, infertility, cystic ovaries, and dysmenorrhea. Each disorder has been attacked separately with different treatment for each. Surgery has offered the most hope for many of these conditions, because of the unsatisfactory results from endocrine therapy.

Efforts to stimulate the ovaries have been largely unsuccessful. Hypophyseal (pituitary) gonadotropes and chorionic gonadotropes have been used singly and together. Mild roentgen-ray exposure of the ovaries and pituitary gland has been successful in some hands, but is not favored because of its inherent danger. As a result of the difficulty in stimulating the ovaries, substitutive glandular therapy has been used frequently, in the hope that a normal cycle would somehow be established.

Hamblen³ used estrogens in menorrhagia in 1931. Karnaky⁴ in 1940 advocated the use of diethylstilbestrol, a potent estrogenic hormone, for this condition which nearly everyone agrees is caused by an excess of estrin in the body. His argument was that the primary cause of the excess estrin is an unruptured Graafian follicle in the ovary. The ovum does not escape and an anovulatory cycle results. The estrin-containing liquor folliculi continues to be absorbed, and the corpus luteum forms poorly, if at all. Lack of progesterone from the corpus luteum permits the action of the estrin to go unopposed, so that the proper balance between these two hormones is disturbed. Thickened endometrium and excessive menstrual bleeding occur because of the hormonal imbalance.

Karnaky proposed to re-establish this balance, not by "neutralizing" the estrin with progesterone or androsterone in the classical manner, but by destroying the cysts in the ovaries through the use of large doses of diethylstilbestrol. The suggested dose, 5 mg. daily for twenty days, depresses action of the pituitary gland. It is believed that the unruptured Graafian follicle is resorbed, because of lack of prolan stimulation from the pituitary. The sudden withdrawal of the diethylstilbestrol at the end of the twenty days allows the action of the pituitary to resurge rapidly. This may produce an unusual stimulation of the ovary naturally.

On the basis of the foregoing theory, it was decided to give diethylstilbestrol in 5 mg. doses to any patient who had any of the so-called functional ovarian disturbances. These disturbances were interpreted to include dysmenorrhea, simple cystic ovaries (the "medical cysts" of Crossen¹), irregularity in menstrual rhythm, menorrhagia, and infertility.

Material

This study has been given impetus by the fact that the women seen in the Army clinics are in the younger age group, in which the disorders of ovarian function are most

frequent. One hundred seven women were studied, all of whom had sufficient complaint to seek medical care for their pelvic disorders. Thirty-one had a single complaint and 76 had two to four of the functional ovarian disturbances. Of these 76, 38 had two complaints, 29 had three, and 9 had all four. Some were in service in the Army, but the larger number were wives of servicemen. Only eight of the group were over 34 years of age. At least fifty additional women were treated; but, because of difficulty in follow-up, they have been excluded from this study.

Method

After a careful history and physical examination, one 5 mg. tablet of diethylstilbestrol was given orally each day for twenty days. It was started at the end of a menstrual flow to avoid interrupting the cycle, and at bedtime to minimize nausea. The patient was instructed to report any unusual symptom and to return for re-examination at the end of the twenty-day period. At this time her symptoms were reviewed, and the pelvic examination was repeated. No other medication was given. Subsequent visits were governed by the patient's need for examination. A questionnaire was sent to those who had left the vicinity. These patients were followed sufficiently long to observe the results of therapy, more than seven months in the majority of cases. Ten per cent had endometrial biopsies at the start of the case, but because the patients changed their residence frequently, it was not possible to follow the ovarian function by repeat biopsies.

Results

Immediate Reaction to Diethylstilbestrol.—Approximately one-half of the patients had some nausea for the first two or three days. Nine and three-tenths per cent stopped taking the drug because of extreme nausea. If the patient persisted in taking the medication for three or four days despite the nausea, this symptom was not noted during the rest of the period of treatment. Very few patients had some nausea during the entire course. It was found that if 5 mg. of diethylstilbestrol produced extreme nausea, 0.1 to 1 mg. also produced extreme nausea with no chance of building a tolerance to the larger dose. The breasts became more sensitive and fuller in most instances, and a marked increase in secretion from the cervical glands occurred. Some patients noted thickening of the waist and puffiness of the ankles. The general symptomatology was that of early pregnancy, and suggests the possibility of a causal relationship between high estrin in early pregnancy and the symptoms which are considered to be physiologic at that time. Nervousness was often relieved during the treatment. Uterine bleeding during the course of therapy was unpredictable. A menstrual flow, due during this time, sometimes came as usual and sometimes was prevented from coming. It was normal, or abnormal in amount and duration. Because this aberration upset the patient's peace of mind, therapy soon was started at the end of a menstrual flow. Withdrawal bleeding occurred within eight days in all cases except two. One of these became pregnant during treatment and the other suffered from hypomenorrhea, secondary to "temporary" roentgen-ray castration which had been done some years previously for menorrhagia. This withdrawal bleeding varied from one day to two weeks and varied in amount and duration. Although it was almost always painless, its nature gave no clue to the subsequent menses. The next menstrual flow occurred twenty-eight to thirty-five days later and was designated as the first normal menses, i.e., the first bleeding to occur as the result of the cyclical activity of the ovary.

Dysmenorrhea.—Seventy patients complained of dysmenorrhea. This was classified severe if the pain necessitated bed rest, but if the pain required analgesics without bed rest, it was called moderate. Thirty-seven patients had either no pain or only an occasional cramp and were considered not to have dysmenorrhea. Table I shows the results in cases of dysmenorrhea, several months after the original course of therapy, when the patient was not taking any medication of any kind. Of the 55 who completed the course of treatment and were followed up successfully, 17, or 31 per cent, were completely relieved; 14, or 25 per cent, were changed from severe to moderate; and 24, or 44 per cent, were not helped. Three patients with severe dysmenorrhea were completely relieved for several months, but two of these had relapses due to environmental change and the third due to a heavy factory job. These were included in the moderate improvement column. A total improvement of 56 per cent, while not ideal, is encouraging in this difficult problem. Bleeding during the course and the withdrawal bleeding at the end of the course of therapy were almost always painless, as has been shown by many workers, with smaller doses of estrogens. It is subsequent menses that prove the success or failure of the treatment.

TABLE I. EFFECT OF DIETHYLSTILBESTROL ON DYSMENORRHEA

	NO IMPROVE- MENT	MODERATE IMPROVE- MENT	COMPLETE RELIEF	NOT KNOWN	INCOM- PLETE TREATMENT	TOTAL
Severe dysmenorrhea	16	14	11	5	5	51
Moderate dysmenorrhea	8	0	6	3	2	19
TOTALS	24	14	17	8	7	70
Total improved	31					
Total unimproved	24					
No dysmenorrhea			34		3	37
						107

Cystic Ovaries.—Almost 50 per cent of patients in the series had enlargement of one or both ovaries. These varied in size from 3 to 15 cm. in diameter. The 3 cm. size was a round, tense, cystic ovary, not much larger than normal, but definitely abnormal in shape and texture. In thirty-three of fifty-one cases in which ovaries were enlarged, one or both ovaries exceeded 5 cm. in diameter. Pelvic pain, which was a prominent feature, caused 28 of the 51 patients to seek relief and necessitated hospitalization for three of these. Crossen¹ and other writers have stressed the need for conservatism in treating these cases. Many simple cysts disappear spontaneously, as any gynecologist knows. Table II shows the results after the course of diethylstilbestrol. Only 6 of 47 patients who completed the course of treatment still had adnexal enlargement, but only two proved to be cystic ovaries which had not responded to treatment. The other four included three inflammatory masses and one dermoid cyst, which was removed surgically. Four patients had recurrence of the cystic condition of the ovaries, but none of these was symptomatic. The ovaries were usually normal at the end of twenty days although some larger ones took six to twelve weeks to reach normal size. Reduction in size was apparent, after three weeks, even in these.

TABLE II. EFFECT OF DIETHYLSTILBESTROL ON CYSTIC OVARIES

Returned to normal	37
Not known	4
Incomplete treatment	4
No improvement	6
	51
<i>No Improvement</i>	
Dermoid—operated	1
Inflammatory disease—operated	1
Inflammatory disease—suspected	2
Cystic ovaries—operated	2

TABLE III. EFFECT OF DIETHYLSTILBESTROL ON MENSTRUAL DISORDERS

	NORMAL	IM- PROVED	NO IMPROVE- MENT	NOT KNOWN	INCOM- PLETE TREAT- MENT	TOTALS
Less than 24-day cycle and/or profuse flow	13	7	7	6	2	35
More than 35-day cycle	5	7	6	0	1	19
Cycle 24 or less, to 35 or more days in same patient	4	1	1	0	0	6
Continuous bleeding up to 120 days	13 (stopped in 1 to 4 days)		1	0	0	14
Totals	35	15	15	6	3	74*

*Includes one patient counted in two columns.

Menstrual Disturbances.—By far, the commonest type of menstrual disturbance was excessive or too frequent flowing, including 49 of 74 cases. These were further divided into 14 cases of continuous bleeding and 35 cases of too frequent or too profuse periods. Although many patients with continuous flowing had bled for several weeks, they ceased flowing in one to four days with one exception. This result, with others of this group, is shown in Table III, and compares favorably with results obtained in constant bleeding by the Durham, North Carolina, group.^{2, 5} One patient who was a failure in this hypermenorrhea group, and is over

40 years of age, is now in Colorado where she expects soon to have a radium-induced menopause. Another failure had an intramural, uterine fibroid, 3 cm. in diameter, and a solitary cystic ovary. The ovary returned to normal size, but a hysterectomy was necessary to control the excessive monthly flow. Only seven cases, including the two just mentioned, could be listed as unimproved. Half the patients with menorrhagia had cystic ovaries. Of the patients whose menstrual interval was more than thirty-five days, twelve became normal or improved, and six remained unimproved. One of six patients with markedly irregular cycles was not improved. Seventy per cent of all menstrual disturbances were completely relieved or greatly improved.

Infertility.—The question of fertility was added to this study when it was seen how often infertility occurred in relation to the other "functional" complaints. Because of the temporary tenure of these patients, the majority were not interested in a complete infertility investigation. Consequently, results shown in Table IV do not represent an exhaustive study. Since many patients were unmarried and some married women practiced contraception, the thirty-seven cases do not represent a true incidence of infertility in the group. All thirty-seven women had remained infertile at least ten months. Following the diethylstilbestrol course, several women who had been "infertile" less than ten months, became pregnant, but these could be considered coincidental and were excluded from tabulation. Only twenty-three patients reported who were living with their husbands and who had completed their course of treatment. Seventeen were not pregnant. Of these, one is to be operated upon for persistent adnexal masses, probably inflammatory. Two others have husbands whose sperm is totally inadequate. One of six who became pregnant had a husband whose sperm was inadequate, but improved after hormonal therapy. Two women are still pregnant; two had normal children; one had a stillborn child; and one had an abortion at three months after a long auto trip.

TABLE IV. EFFECT OF DIETHYLSTILBESTROL ON INFERTILITY

Not with husband, after treatment	4	
No pregnancy	17	74%
Pregnancy	6	26%
Not known	7	
Incomplete treatment	3	
Total	37	100%

Discussion

The most encouraging feature of this study is that favorable results persisted for several months after cessation of all medication. Whether this is a true ovarian stimulation cannot be said from this purely clinical work. Endometrial biopsies and hormonal assays before, and again a month after the conclusion of treatment might clarify this point.

It has long been known that there is a relationship between ovarian function and nervous activity. In the menopause, failing ovarian function seems to produce "nervousness." On the other hand, emotional shocks often induce amenorrhea or menorrhagia. Some patients in this series voluntarily reported a great improvement in their nervousness following treatment. Some other patients, who were very nervous, showed no improvement either in their nervousness or in their pelvic complaint. No conclusions can be drawn from this, but it again emphasizes the close relationship between the ovaries and the nervous system.

Improvement in patients with dysmenorrhea was maintained in 56 per cent without altering the cycle each month. This compares favorably with other methods of control, but is not to be considered the final solution of the difficulty. Estrogens have been shown by others to relieve dysmenorrhea, if given during the first half of the cycle each month. But an anovulatory cycle which is not desirable is produced. The single course of large doses of diethylstilbestrol probably produces only one anovulatory cycle and so overcomes that objection.

Cystic ovaries responded readily to the medication used. No doubt many would have become normal without treatment, but many patients had been ad-

vised elsewhere to have the pelvis explored surgically. Surgery for enlarged ovaries should not be advised without re-examination after a few weeks. This waiting period can be used for a course of diethylstilbestrol. If the ovary has not been reduced in size, surgery is indicated.

Many writers on hormonal subjects do not distinguish between the effect of small and large doses of diethylstilbestrol. It is well established that small doses cause thickening of the endometrium and, eventually, bleeding. I have confirmed the work of Karnaky⁴ and of the Durham group^{2, 5} by arresting prolonged uterine bleeding with large doses of this substance. It is less effective in regulating abnormal length of the menstrual cycle, but is more successful than many reported techniques.

No definite statement can be made as to the value of this medication in infertility except that it is worthy of further study.

The high percentage of success achieved in using a single type of treatment for multiple functional complaints suggests that they have a single cause, a malfunctioning ovary, and that the various disorders considered are different manifestations of the same underlying pathologic physiology.

Summary

1. Diethylstilbestrol was given orally in doses of 5 mg. daily for twenty days to 107 women with 232 functional ovarian complaints. Symptoms resulting from its use were described.

2. Partial or total relief was obtained in 56 per cent of patients with dysmenorrhea.

3. Ovaries returned to normal size in 37 of 47 patients with cystic ovaries.

4. In 13 of 14 patients, continuous uterine bleeding ceased after one to four days. Of all menstrual disturbances 70 per cent were partially or entirely corrected.

5. In an admittedly incomplete study on infertile women, 26 per cent conceived.

6. It was suggested that all the disorders considered are but different manifestations of a malfunctioning ovary. From a clinical standpoint, diethylstilbestrol, in the dosage used, corrected the manifestations of ovarian dysfunction in a majority of the cases.

References

1. Crossen, H. S., and Crossen, R. J.: *Operative Gynecology*, ed. 5, St. Louis, 1943, The C. V. Mosby Co.
2. Cuyler, W. K., Hamblen, E. C., and Davis, C. D.: *J. Clin. Endocrinol.* 2: 438, 1942.
3. Hamblen, E. C.: *Endocrinology* 15: 184, 1931.
4. Karnaky, K. J.: *South. M. J.* 33: 1285, 1940.
5. Turner, V. H., Davis, C. D., and Hamblen, E. C.: *J. Clin. Endocrinol.* 3: 453, 1943.

MESENTERIC THROMBOSIS COMPLICATED BY DERMOID CYST

RUTH ELIAS LESII, M.D., F.A.C.S., FAYETTEVILLE, ARK.

(From the Fayetteville City Hospital)

ALTHOUGH cases of mesenteric thrombosis are relatively few, they are important out of proportion to their number because of their severity and grave prognosis. An early diagnosis is often precluded because initial symptoms are not indicative of the condition and could be those of other intra-abdominal emergencies.

A few presenting symptoms, occurring in practically all recorded cases, suggest occlusion of a mesenteric vessel strongly enough to warrant a correct diagnosis. The following case report and a brief summary of the literature are offered to emphasize these symptoms in order to encourage a better prognosis. In addition the interesting complication of a dermoid cyst arising in the left ovary is described.

Persons of any age may be attacked by mesenteric thrombosis, but most cases occur about the time degenerative diseases begin. The average age is usually from 43 to 45 years, males predominating by about 40 per cent.

Mesenteric occlusion may be arterial, venous, or a combination of both. In arterial occlusion either embolism or thrombosis may precede, while in venous occlusion thrombosis has always occurred. The resulting infarction usually leads to necrosis of the adjacent intestinal wall, with resulting peritonitis and gangrene. The affected bowel then becomes dark red, with swollen mucosa and a lumen filled with hemorrhagic material.

The intestine involved may be anywhere from a few inches to the entire small bowel. Brown mentions the average length of affected intestine in 22 patients who recovered as 38.1 inches, and as 102.4 inches in 39 who died.

Causative lesions of venous and arterial occlusions of the mesenteric vessels are many. Among them are portal obstruction, cardiac conditions, septic abdominal lesions, intimal lesions, peripheral sepsis, degenerative diseases such as arterio-sclerosis, and mechanical damage arising from hernia, surgery, and obstruction. Ochsner includes long period alcohol consumption as causative. Green records fatigue and prolonged emotional strain as etiological factors. In many cases there is no apparent cause.

In its clinical features, mesenteric thrombosis is characterized primarily by pain, which may be dull and cramping or sudden and severe. It is usually centrally located, incessant, and not accompanied by muscular spasm or extreme tenderness before gangrene and peritonitis develop. Giamarino states that the pain tends to become colicky in about 50 per cent of the cases.

Localization of pain does not occur early and therefore rarely gives a definite clue for early diagnosis. When the pain is localized, it is more often in the lower right quadrant. In the following case and two previously reported in the literature, the onset of pain was in the lower left quadrant. Klemp believes that thrombosis of the inferior mesenteric vein gives rise to pain predominately on the left side, while thrombosis of the superior mesenteric vein produces pain mainly on the right side.

Three points upon which authorities agree as distinctive features of the pain of mesenteric occlusion are: (1) that it is more severe than the clinical findings warrant; (2) that it is not alleviated by morphine; and (3) that there is much less tenderness than would be looked for with such intense pain.

Various other symptoms may be found in mesenteric thrombosis. Vomiting is more common in arterial than in venous occlusion. Whittaker and Pember-ton say that it occurred in about 75 per cent of the cases of arterial and combined arterial and venous occlusion, and in 50 per cent of the venous cases. Shock is another symptom that is not always present, but it is marked in fulminating cases and may appear in others in proportion to the mesenteric involvement. Constipation or diarrhea accompanied by bloody stools may be coincident, the former being more common.

Pallor and restlessness are often noted at the onset, but they are more marked later, being less evident in the early stages of venous than in arterial cases. Peristalsis is diminished, free fluid can usually be detected in the abdomen, and at times palpation demonstrates swollen intestinal coils. Rigidity and distention, if they do appear, are late symptoms. Distention is probably present in less than half the cases and is usually moderate, being more frequent in venous than in arterial thrombosis.

The leucocyte count and pulse rate furnish valuable clues to mesenteric occlusion because they are both almost uniformly high out of proportion to the temperature, which, like the blood pressure, is usually low. There may be a leucocytosis of 35,000 or more in arterial occlusion, while in venous occlusion there is a leucocytosis of approximately 20,000. The rapid pulse tends to become thready and slow, as the disease progresses.

The differential diagnosis includes ruptured peptic ulcer, various blood dyscrasias, and pelvic conditions such as ectopic pregnancy and torsion of pedicle of ovarian cysts.

The treatment of mesenteric occlusion is, of necessity, surgical. Exploratory laparotomy should be undertaken as soon as the condition is suspected, because the surgical risk greatly increases with the development of gangrene of the intestine. The affected portion of the gut, or the part nourished by the occluded vessel, must be resected and a fan-shaped portion of mesentery removed, following which anastomosis of the intestine and union of the mesenteric edges is accomplished. The postoperative treatment is supportive.

Case Report

The patient, Mrs. V. G., white, aged 39 years, was seized with severe pain in the lower left portion of the abdomen while eating her evening meal about 6 P.M. on May 31, 1944. A physician was summoned when nausea and vomiting occurred. The pulse was of good quality, and the patient did not seem shocked. No relief from pain being obtained from $\frac{1}{4}$ grain of morphine and $\frac{1}{150}$ grain of atropine and 3 grains of nembutal, she was sent to the hospital by ambulance. On admission to the Fayetteville City Hospital at 8:30 P.M., the patient was in excruciating pain localized in the lower left quadrant. She was moaning and had poor control of herself. The patient had had dysuria and pain in the left lumbar region on the preceding day. She had been married sixteen years. Her husband was living and well. She had two children, ages 15 and 4 years, both normal pregnancies and deliveries. There had been no serious illnesses, but for the past two years she had been extremely nervous and morose, and refused to live with her husband when he accepted a position in another city. Sixteen years previously, the right tube, ovary, and appendix were removed surgically. Menstrual periods had been regular with onset at 13 years of age and interval of twenty-eight days. The last menstrual period was May 16, 1944. The family history was irrelevant.

On physical examination, the face was colorless, lips blanched, and gums pale. The tongue was clear, the pharynx was not congested, and the tonsils had been removed. The

thyroid was palpably enlarged. No cervical adenopathy was present. The thorax was well developed. The heart was not enlarged, but the sounds were slow, weak, and of poor quality. No murmurs were present. Lung expansion was good, with the note resonant to percussion. Respirations were 25. There were no râles on cough. The abdomen was relaxed, with rounded contour. A midline scar from the symphysis to the umbilicus was present. No masses were palpable. Extreme tenderness was elicited over the lower abdomen above the bladder, particularly on the left side, and with deep pressure over the left lumbar area. Pelvic examination showed good perineal support, and no discharge or bleeding. The cervix was in midposition, not eroded, and the fundus small and anterior. There was fulness in the cul-de-sac and pain with upward pressure in this area. No masses were outlined in either fornix. The extremities showed no pathology.

Following admission to the hospital, the patient was given $\frac{1}{2}$ grain of codeine with 2 grains of sodium luminal hypodermically. No relief followed. About 10 P.M. she became extremely shocked, cold and clammy, with pulse almost imperceptible. She rallied somewhat with external heat, but the pulse was extremely slow and weak. At this time the red blood count was 4,030,000, hemoglobin 100 per cent, leucocytes 15,050, with a differential of 88 segmented, 1 stab, and 11 lymphocytes. A catheterized specimen of urine was straw colored, reaction 7.5, specific gravity 1.020, faint trace of albumin, 1 plus acetone, with the microscopic examination negative.

The abdomen, which had been soft on admission, became rigid in the lower portion. In the lower left quadrant an indefinite mass extending about 5 fingerbreadths above the symphysis could be palpated. By vaginal examination a mass could now be palpated in the left fornix.

The patient became more restless and her condition was grave. Consultation was obtained and exploratory laparotomy was advised. A differential diagnosis was made of (1) left ovarian cyst with torsion of the pedicle and hemorrhage into the cyst, and (2) ruptured ectopic pregnancy in the left tube.

Laparotomy was performed about 1 A.M., June 1, 1944. Prior to surgery the patient was given 500 c.c. Beclysyl* intravenously. Nitrous oxide with oxygen was administered as the anesthetic over a period of one hour and twenty-two minutes. The blood pressure ranged from 90/40 to 100/60, the respiration rate was 20 to 30 per minute, and the pulse rate was about 70 per minute. Fifteen cubic centimeters of adrenal cortical hormone† and 500 c.c. Beclysyl were given to combat shock during the operation.

A midline incision was made from the symphysis to the umbilicus, to the left of an old scar. When the peritoneal cavity was opened, a small amount of serosanguineous fluid appeared and a gangrenous loop of ileum presented in the wound. About 48 inches of gut were clamped off and the affected portions excised, together with a V-shaped section of the mesentery. After the raw edges of the mesentery were united with continuous intestinal suture to control hemorrhage, a Murphy button was placed in the usual manner in each end of the intestine and the buttons united. Further approximation of the intestine was accomplished with a continuous suture uniting the serosa around the circumference of the button. Five grams of sulfanilamide powder were sprinkled in the wound, a flaccid drain inserted, and closure made in layers. The wound drained a large amount of serosanguineous fluid and the fatty tissue and skin bled freely, hemorrhage not being entirely controlled. The uterine fundus was anterior, the right tube and ovary had been removed, and the left tube and ovary were apparently grossly normal except for adhesions in that area.

The pathologic report showed a hemorrhagic infarction of the intestine.

The patient had a stormy postoperative course. Nasal suction was continued for about ten days, during which time the rectal temperature remained around 103° to 104° F., and the pulse was 120 to 140. Most of the time the patient was irrational. Treatment was supportive. On June 10, fecal matter began to drain from the wound and the abdomen was distended. Three transfusions of 500 c.c. of citrated blood were given by the indirect method on June 14, 15, and 16. Even as late as the twenty-fourth postoperative day the abdomen was still distended, the nasal tube was inserted at intervals, and the patient at times would become cold and clammy as if in shock. The superficial sutures for the most part sloughed out, and the deep sutures were removed on July 13, the forty-third postoperative day. On July 14 the patient sat up in a chair. On July 19 the Murphy button was removed manually

*Abbott Laboratories.

†Upjohn.

from the rectum. The patient was discharged July 23, the fifty-third postoperative day. At this time the wound was still draining some fecal material, but the patient was having normal stools.

The course was uneventful following her return home, the fecal fistula closing in about two weeks. From then on the patient was able to resume most of her usual housework and had no complaints. Upon coming into the office, Sept. 29, 1944, for routine follow-up, a pelvic examination disclosed a large mass in the pelvis. The abdominal wound was entirely healed, and there were absolutely no complaints indicative of the growth, although the patient stated that she had seemed to gain weight excessively for the past month. The menstrual periods and bowel movements were normal.

The mass steadily enlarged in size, but operation was not advised until later because of the patient's recent critical condition. Operation was undertaken, however, when difficulty in voiding became apparent. The patient was admitted to the hospital again on Nov. 17, 1944. The three days prior to surgery she had nausea, vomiting, and diarrhea, with temperature of 100° to 102° F. Physical examination on admission was essentially negative except for the pelvic condition. The vaginal examination showed good support. The examining finger met a mass that made the cul-de-sac protrude, practically filling the vagina. The cervix was pushed forward under the symphysis pubis and was extremely difficult to palpate, and impossible to expose to view with the speculum. The mass was densely adherent, tender, and seemed to have two portions, the one on the right side extending upward to a greater extent than the one on the left.

Operation was performed on Nov. 20, 1944. The incision had to be made far to the right of the midline to avoid the old scars. Upon entering the peritoneal cavity, a large dermoid cyst was found supplanting the left ovary, adherent to the uterus, tube, omentum, and intestines. The uterus was drawn over to the right side, and the mass, which at first was impossible to outline, seemed to push the uterus and bladder forward and occupy the entire pelvis. The cyst extended deep into the vagina, particularly on the right side, and was adherent throughout. In breaking up the adhesions, the cyst wall was ruptured and a large amount of gray, cheesy-looking material and many long hairs were liberated. The tube and pedicle of the cyst were twisted twice at the base, and this area was clamped. In freeing the remainder of the cyst, a large abscess cavity posterior and to the right was entered and drained. The stump of the broad ligament and tube was ligated. Five grams of sulfanilamide powder were dusted into the area. A flaccid drain was put deep in the right side of the pelvis and the abdomen was closed in layers.

The patient reacted well from the anesthesia, and the postoperative progress was uneventful except for delayed healing of the lower portion of the wound. The drain was removed at the end of forty-eight hours, the superficial sutures on the tenth day, and the deep sutures on the twelfth day. The patient left the hospital on the fourteenth postoperative day, with the lower portion of the wound unhealed, but otherwise in excellent condition. At the present time, three months after the operation, the patient seems to be entirely well.

Discussion

This case of mesenteric thrombosis, later complicated by a dermoid cyst of the left ovary, is offered with a brief recapitulation of the literature to emphasize the presenting symptoms common to the majority of such cases, and to state the belief that if the treatment is always surgical with no preface of conservatism and delay, the mortality will be lowered.

In the presence of a pain that indicates an intra-abdominal catastrophe localized to either lower quadrant, one should remember that mesenteric occlusion can be localized in either quadrant when the affected portion of the bowel forms a mass, and can be readily confused with pelvic conditions, such as ovarian cyst and ectopic pregnancy.

Upon considering the possible sources for the mesenteric thrombosis in our case, the most likely causes seem to be the fact that the patient had entered the age of degenerative disease and that she had been under emotional strain for two years.

The occurrence of the cyst was probably unrelated to the mesenteric thrombosis, but it is interesting to speculate whether elements contributing to the

growth of the cyst were present in sufficient amount at the time of the first operation to have been the causative factor in the forming of the embolus.

Summary

1. The etiology and clinical picture of mesenteric thrombosis is offered from our case report and from a brief review of the literature.

2. Etiologically, mesenteric occlusion can result from mechanical damage, peripheral sepsis, portal obstruction, inflammatory abdominal lesions, degenerative diseases, cardiac diseases, and less definite causes such as excessive alcohol consumption and emotional strain.

3. The commonest early symptom is intense pain, not relieved by morphine, and out of proportion to the mild clinical findings.

4. Other symptoms may include pallor, restlessness, vomiting, constipation or diarrhea, tenderness, rigidity, shock, leucocytosis, and rapid pulse rate, low temperature and blood pressure, with a possible rise in temperature as a very late symptom.

5. When the pain becomes localized in either of the lower abdominal quadrants it can readily be mistaken for a gynecologic condition.

6. In our case, there was no causative lesion determined. The most likely factors seem to be the patient's age and the emotional state. The early appearance of the cyst after the first operation suggests a mere possibility that it may have been the cause of the embolus.

7. The present high mortality of this disease can be reduced by immediate surgery upon suspicion of the condition.

References

1. Brown, M. J.: *Am. J. Surg.* 49: 242, 1940.
2. Dunphy, J. E., and Whitfield, R. D.: *Am. J. Surg.* 47: 632, 1940.
3. Ficarra, Bernard J.: *Am. J. Surg.* 65: 168, 1944.
4. Geis, Arthur F.: *Am. J. Surg.* 65: 268, 1944.
5. Giamarino, Henry J., and Jaffe, Samuel A.: *Arch. Surg.* 45: 647, 1942.
6. Hertzler, Arthur E.: (Christopher) *Textbook of Surgery*, Philadelphia and London, 1942, W. B. Saunders Co. p. 1081.
7. Klemp, Wilhelm: *München. med. Wchnschr.* 87: 908, 1940.
8. Larsen, G. M.: *Surg., Gynec. & Obst.* 53: 45, 1931.
9. Luke, Josephus C.: *Lancet* 244: 552, 1943.
10. Mathias, Marion L.: *J. South Carolina M. A.* 36: 97, 1940.
11. McBee, Paul: *South. Med. & Surg.* 99: 398, 1937.
12. Moore, Thomas: *Brit. J. Surg.* 28: 347, 1941.
13. Pollock, L. W.: *Texas State J. Med.* 33: 556, 1937.
14. Raven, Donald W.: *Lancet* 233: 1131, 1937.
15. Whittaker, Lorin D., and Pemberton, John deJ.: *J. A. M. A.* 111: 21, 1938.
16. Ochsner, W., and Penny, J.: *New Manual of Surgery*, Chicago, 1915, Cleveland Press.

26 NORTH COLLEGE AVENUE.

A SEVEN-YEAR REVIEW OF ECLAMPSIA WITH SPECIAL REFERENCE TO TREATMENT WITH VERATRUM VIRIDE

LT. (J.G.) GEORGE G. GREENE (MC) USNR,* QUANTICO, VA.

(From the Department of Obstetrics and Gynecology of the University of Tennessee School of Medicine and the John Gaston Hospital, Memphis, Tenn.)

DURING the past fifty years innumerable methods of treatment for eclampsia have been advanced. Some of these have held their place in the armamentarium but many have fallen by the wayside. It is one from the latter group that, it seems, should still have a definite place in the therapeutic role, namely, *Veratrum viride*.

It is true that this was not discarded by all and that many general practitioners in the South and even some of the Medical Centers continued to use this routinely. I refer particularly to the Department of Obstetrics at the University of Cincinnati. In the October, 1940, issue of the *Journal of the American Medical Association*, Dr. Flemming and Dr. Bryant, of the Department of Obstetrics at the University of Cincinnati School of Medicine, reported a study of 120 cases on which *Veratrum viride* had been used with only 1.6 mortality, and even those included in the mortality group, on further investigation, could hardly be included in the group of failures. It was from this report that further interest was aroused for this particular method of treatment.

Soon after joining the resident staff of Obstetrics at the John Gaston Hospital, Memphis, Tennessee, in July, 1941, permission was obtained from Dr. W. T. Pride, Chief of the Department of Obstetrics and Gynecology at the University of Tennessee School of Medicine, to begin the use of this drug in the treatment of eclampsia where a number of such patients are encountered each year. We used very much the same method as that outlined by Dr. Flemming and Dr. Bryant except for minor modifications at times which will be mentioned later in this report.

After using *Veratrum viride* for approximately one year with uniformly good results, it was suggested by Dr. J. R. Rheinberger, Associate Professor of Obstetrics, that we make a seven-year study of treatment of eclampsia as followed in our hospital, using for a comparative study the last year, during which time *Veratrum viride* had been used. This was done and our report deals with the years 1936 to 1942 inclusive. During these seven years 150 cases were diagnosed as eclampsia of pregnancy.

Methods and Treatment

We group our toxemias in Grades I, II, III, and IV. The Grade I were those with only mild symptoms of toxemia; Grade II, those of the pre-eclamptic group; Grade III, those of the definite eclamptic group; and Grade IV, those who may have convulsions and appear at first to be true eclampsia, but on further investigation reveal definite kidney damage which may have been present prior to the pregnancy. It is my opinion that our method of treatment has no definite place and is of little value in Grades I, II, and IV, only being of value in Grade III, true eclampsia.

We do not hesitate to use the drug in questionable cases of eclampsia where the diagnosis is not certain. We have our patients constantly attended, usually by senior medical students, until the patient is rational.

*Family physician for the Quantico Marine Base.

Instructions for Treatment of Pre-eclampsia and Eclampsia

1. Give 5 to 10 minims (0.3 to 0.6 c.c.) of *Veratrum viride* immediately; repeat every fifteen minutes unless the pulse rate is below 60 or the blood pressure is below 120 systolic; thereafter, until the patient is conscious, repeat in 3 to 10 minim (0.2 to 0.6 c.c.) doses if the pulse rate goes over 80 or the blood pressure over 150 systolic; after the patient is conscious and cooperative, give 3 to 10 minim doses if the patient is nauseated or has severe headache, marked visual disturbances, or epigastric pain or convulsions.
2. Give 6 c.c. of 50 per cent magnesium sulfate by deep injection immediately, 4 c.c. every six hours for four doses, and then 4 c.c. every twelve hours for four doses.*
3. Give 500 c.c. of 20 per cent dextrose intravenously at once; repeat every eight hours until consciousness returns.
4. Catheterize and give a soapsuds enema immediately.
5. Check the pulse and blood pressure hourly as long as coma persists, then every two to four hours while the patient is awake.
6. Force fluids (3,500 c.c. daily) by mouth as soon as possible.
7. Give no sedatives except for extreme restlessness or labor.
8. Institute a diet free of salt as soon as tolerated.
9. Measure the fluid intake and the urinary output; examine the urine daily for albumin.

TABLE I. TABULATION OF CASES
1936 to 1942

Negro patients	129
White patients	21
Total	150
1936 to 1941	
Maternal mortality	35 or 26%
Infant mortality	42 or 50%
1942	
Maternal mortality	0
Infant mortality	2 (?) or 6%

Pharmacology of *Veratrum Viride*

Veratrum viride is an alkaloid, and is derived from the roots and rhizomes of hellebore. This plant is indigenous to both Europe and North America. The drug acts as a cardio-inhibitor, vasodilator, and antipyretic. It is toxic in large doses and must be given carefully. Toxic reactions include sudden drop in blood pressure and pulse rate, nausea and vomiting, and eventually coma. Toxic reactions may be counteracted by gastric lavage or atropine in the usual dose. The preparation used was Veratrone† in doses of 3 to 10 minims, given by hypodermic injection.

Comment

Since there are many more Negroes in the South, it was with these that most of our study was made. Out of the 150 cases, 129 were Negro and 21 white, a ratio of nearly 6 to 1. Many of these never attended a prenatal clinic as is well shown here in that 71 of 150 cases were nonclinic patients. Table I shows the comparative percentage mortality in the mothers and infants for the seven-year study. It is to the year 1942 that we wish to pay special attention. However, our cases are only 15 in number and of these, 14 received *Veratrum viride*. With this reduction in number of actual eclampsias, there were still almost 50 per cent that were nonclinic patients. This brings out the important role of prenatal care. It was noted that over 50 per cent of the cases were in women 20 years of age or younger. It occurs to me that this disease, true eclampsia, is far more frequent in women of this age group and is due to the

*In a number of these cases the 50 per cent magnesium sulfate was omitted from our treatment regime, and only the concentrated glucose was used. There did not seem to be any marked difference in response in these cases.

†Parke, Davis & Company.

lack of care. This is especially true in young Negro girls to whom the responsibility of childbearing is of minor significance and is given little consideration.

Of the 150 cases in this review, 104 were primigravidas, revealing that true eclampsia is far more frequent in this group. If those patients diagnosed as eclampsia who have had several children and are in the later years of childbearing are studied carefully, it will be found that a large number of them fall into Grade IV where chronic kidney damage has been present for some time. In this group we do not believe *Veratrum viride* is of much value. In over half of the patients, the onset of eclampsia was in the antepartum period.

During these seven years, every method of treatment known seemed to have been given a chance at one time or another. Many sedatives were used, including morphine, magnesium sulfate, sodium bromide, chloral hydrate, and various barbiturates both orally and intravenously. In the earlier years of this study many supportive measures were given. Gastric lavage was used extensively. Concentrated glucose and even 20 per cent sucrose were used intravenously. On investigation, one of the fatalities was thought most likely due to the latter. Digitalis was given in many cases seemingly as a prophylactic measure. This drug was used in five of the seven years reviewed and is still being used for the same reason in some university hospitals. Salyrgan was used alone and in conjunction with digitalis. In reviewing many of these cases, there was no particular value that could be attributed to its use. This helped to further confirm the idea, already in mind, that digitalis has no place prophylactically or therapeutically in the treatment of eclampsia unless decompensation or auricular fibrillation is present.

In the year 1937 many cesarean sections were done. It was in this year that the mortality reached its highest peak. Nine sections were done out of 20 cases (45 per cent) for that year. Seven of the nine patients expired. Five of the seven cases were treated in the hospital for only twenty-four hours or less before operation was performed. All of these expired. This emphasizes the urgent need for control of the eclampsia before any operative measure is attempted.

We had fifteen cases for 1941 to 1942. Fourteen of these cases received *Veratrum viride*. All of them recovered. We attempted to treat our patients without giving any morphine or barbiturates. We do not feel that a definite sedative is indicated unless the patient is in labor. In some instances they were given through error. Here we feel that paraldehyde per rectum is the drug of choice. It was found that after treatment had been started, 50 per cent or more of our patients did not continue to have any convulsions, at most only two convulsions, and that in a short period of time the patient would be rational and responding to questions.

We feel that no attempt at delivery should be done until the convulsions have been controlled and the patient is rational for one or two days. We have found that a number of these cases will go into labor spontaneously during this period and, if not, that induction of labor can be brought about by the simpler methods, such as medical inductions or some minor operative method such as rupturing of the membranes. A very small number may not respond to any of these. If the patient is a primipara near term, with a closed, thick cervix, a cesarean section can be considered and performed rather safely, provided the eclamptic state has been controlled for a time, but the patient is beginning to show evidence of returning to her former condition by blood pressure rise, increase in albumin and casts in the urine. We do not like to use bag inductions in the primiparas for this or any other reason.

If the patient shows symptoms of severe reactions to the drug such as were mentioned above, we think it best to discontinue this treatment and resort to some other measure.

Since the report on the cases of 1942, we have used this method of treatment and are continuing its use. We had one patient in 1943 who did not respond to our routine, and expired. Altogether, the treatment has continued to prove very successful. We have varied the routine and have tried leaving out the 50 per cent magnesium sulfate intramuscularly, and it would appear from the small number of cases so treated that results were probably as good. This was done at the suggestion of Dr. J. R. Rheinberger.

Conclusions

1. *Veratrum viride* has a very definite place in the treatment of eclampsia.
2. Its greatest usefulness is in true eclampsia.
3. If toxic reactions are shown, discard its use completely for that particular case.
4. No operative procedures should be instituted until convulsions are controlled and the patient is rational.
5. Digitalis has no place as a prophylactic drug for the heart, and its indications are those recognized by the cardiologist.
6. Eclampsia is a complication of pregnancy prevalent mostly among the young Negro woman in the South as the result of improper prenatal care.

I wish to acknowledge the assistance given by Dr. Everette Gustafson in compiling the material and preparing this report for publication.

CONTINUOUS CAUDAL ANALGESIA IN CURETTAGE FOR ABORTION

CHARLES W. NEWTON, JR., M.D., AND GEORGE J. ANDROS, M.D.
ANN ARBOR, MICH.

(From the Department of Obstetrics and Gynecology, University of Michigan Hospital)

THE prevention of blood loss during evacuation of the uterus by dilatation and curettage in therapeutic abortion and in incomplete abortion has long been recognized as an important factor in the control of morbidity and mortality. In hope of decreasing blood loss in these cases, we have in the past eight months employed continuous caudal analgesia in all instances except in the presence of recognized contraindications to caudal technique.

Choice of this technique stems from the observation that blood loss in the third stage of labor managed under continuous caudal analgesia generally is markedly reduced. The decrease in blood loss is attributed to increased contractility of the uterus. In contrast to the effect produced by general anesthetic agents, the motor elements of the active contractile portion of the uterus are not inhibited under the caudal technique if the analgesic effect is kept below the sixth thoracic segment. Cervical tissues, on the other hand, are relaxed through inhibition of their motor innervation.

Appreciating the uterine relaxing effect of general anesthetic agents, Taussig¹ recommended the use of local infiltration of the broad ligaments in cases of this type. Petersen² reported the utilization of spinal anesthesia in therapeutic abortion.

Technique

The technique used by us is based upon the method originally described by Hingson and Edwards.³ Preoperative medication in the form of 0.2 Gm. pentobarbital sodium (Nembutal) is administered orally approximately thirty minutes before the patient is taken to the anesthetic room. With the patient on her abdomen, the lower back is surgically prepared and draped. After local infiltration of the skin, a malleable steel needle is inserted into the sacral canal through the sacral hiatus. When it has been determined that the needle is properly placed, a test dose of 8 c.c. of 1.5 per cent metycaine in Ringer's solution is injected. After a ten-minute period of observation, and in the absence of signs of spinal anesthesia, an additional 22 c.c. of the analgesic agent are injected, and the patient is placed immediately upon her back. Care must be taken to prevent displacement of the needle. The operating table is tilted into 5 degrees Trendelenburg position, the patient's feet are held upward for two or three minutes, following which the legs are suspended by stirrups in lithotomy position. After an interval of about ten minutes the level of analgesia on the abdominal skin is tested by means of a sharp needle. Blood pressure is checked at five-minute intervals during the entire procedure.

The need of subsequent injections of the analgesic agent is determined by the rapidity with which the analgesia progresses upward on the abdominal skin and the height at which it is stabilized. It has been our experience that an additional 10 to 20 c.c. injection is necessary in fifteen to twenty minutes. This usually carries the level of analgesia to the eighth or ninth thoracic segment. Some patients will experience pain when the curette is passed along the top of the fundus unless analgesia is established as high as the ninth thoracic segment.

During the operation an anesthetist is in constant attendance at the head of the operating table, checking the patient's blood pressure and noting her reactions. On completion of the operation, the needle is removed and the hiatal area is cleansed with an alcohol sponge. The patient is returned to her room and subsequently watched for delayed bleeding and fall in blood pressure, neither of which has occurred in our series. It is advisable to administer $\frac{1}{6}$ grain morphine sulfate hypodermically before the analgesic effect wears off, to obviate the discomfort of postcurettage uterine cramps.

As will be noted in the accompanying chart, the amount of 1.5 per cent metycaine used has been relatively constant, the smallest total amount injected being 40 c.c. and the largest 70 c.c. The average dose has been less than 55 c.c. This variance in amount necessary to produce satisfactory analgesia is probably due to individual susceptibility to the drug and to the size of the patient. The amount must be regulated by objective and subjective findings.

At first we used vasopressor agents prophylactically to prevent fall in blood pressure resulting from vasodilatation secondary to lumbar sympathetic block. Four patients received 50 mg. of ephedrine sulfate injected into the sacral canal with the preliminary 8 c.c. dose of metycaine, and in one other case 25 mg. of the same drug were used. Intramuscular injection of $2\frac{1}{2}$ mg. of neosynephrin hydrochloride early in the induction was used in two cases and 50 mg. of ephedrine sulfate were used similarly in another case. In the latter part of our series we found that it was not necessary to use a vasoconstricting agent routinely if the operating table was put into 5 degrees Trendelenburg position and the legs of the patient elevated as soon as she was placed upon her back.

The only other supplemental medication used in this series was ergotrate 0.2 mg. given intravenously in six cases in which the uterus felt boggy. In none of these was bleeding excessive. In all but three cases an intravenous infusion of 5 per cent glucose was started preoperatively. This procedure has been routine in cases done under general anesthesia, where blood loss is anticipated.

Clinical Material

In this preliminary report we are presenting 22 consecutive cases curetted under the caudal technique described above. The first case was a therapeutic abortion performed at ten weeks of pregnancy for far-advanced pulmonary tuberculosis. The remaining 21 were incomplete abortions wherein curettage was deemed advisable.

Eleven of the patients were nulliparas and an equal number multiparas. Ages ranged from 18 to 37 years, with the average at 26.6 years.

Duration of the pregnancies ranged from eight to seventeen weeks. The average gestation period in the series was twelve weeks. In the incomplete abortion cases there had been bleeding from three days to six weeks prior to curettage. The average duration of this symptom was thirteen days.

No case of incomplete abortion had to be curetted in the presence of signs of obvious infection in the pelvis. Diagnosis of incomplete abortion was confirmed histologically in all patients by the presence of decidual and chorionic tissue in the scrapings.

TABLE I. SUMMARY OF DILATATION AND EVACUATION UNDER CAUDAL ANALGESIA

PATIENT	AGE (YEARS)	PAR- ITY	GRAVID- ITY	DURATION OF PREG- NANCY (WEEKS)	DURATION OF BLEEDING PREOPER- ATIVELY	AMOUNT OF 1½% METY- CAINE C.C.	SUPPLEMENTAL MEDICATION	BLOOD LOSS (C.C.)
V. G. 544324	37	0	i	10	*	60	None	60
E. H. 510173	24	i	ii	13	11 days	60	Ergotrate 0.2 mg. I.V. Ephedrine 50 mg. into sacral canal	50
M. E. 459794	24	0	ii	12	8 days	60	None	10
E. H. 546063	22	0	i	13	7 days	40	None	40
E. B. 545052	27	v	viii	11	4 weeks	40	Neosynephrin 2.5 mg. I.M.	35
B. G. 521273	23	0	i	8	9 days	55	None	75
M. A. 544918	33	i	ii	17	12 days	45	None	10
A. S. 544878	23	0	i	11	17 days	40	Neosynephrin 2.5 mg. I.M.	50
N. W. 548085	24	i	ii	14	21 days	65	Ergotrate 0.2 mg. I.V.	125
M. S. 550035	22	0	i	11	3 days	40	Ephedrine 50 mg. into sacral canal	30
K. J. 479932	20	ii	iv	16	6 days	55	Ephedrine 25 mg. into sacral canal	25
R. M. 550912	28	iii	v	11	6 weeks	55	Ephedrine 50 mg. into sacral canal	10
R. H. 551345	26	0	i	11	14 days	55	Ephedrine 50 mg. into sacral canal	5
V. M. 517278	23	0	i	12	19 days	40	Ergotrate 0.2 mg. I.V.	30
M. P. 556600	27	iv	v	14	6 days	60	Ergotrate 0.2 mg. I.V.	25
A. H. 429803	29	0	ii	9	20 days	55	None	5
M. S. 189736	36	ii	iii	12	4 days	60	None	5
G. A. 559924	36	vi	vii	15	5 days	55	None	80
M. E. 459794	25	0	iii	9	19 days	70	None	35
S. W. 560594	26	i	ii	13	10 days	60	Ergotrate 0.2 mg. I.V.	35
D. H. 499652	34	iv	vi	12	10 days	40	None	55
R. S. 561008	18	0	i	12	7 days	70	Ergotrate 0.2 mg. I.V. Ephedrine 50 mg. I.M.	40

*Therapeutic abortion for far-advanced pulmonary tuberculosis.

Results

Blood loss in our 22 cases ranged from less than 5 c.c. to 125 c.c. Seventeen of the patients lost 50 c.c. of blood or less, and the average loss per patient was less than 40 c.c.

These figures compare with an average blood loss of 415 c.c. in twelve unselected cases of abortion curetted in this clinic under general anesthesia. In this group blood loss ranged from 75 c.c. to 1,100 c.c.

In the cases of our series as well as in the control group the blood lost from the uterus during the operation was collected in a pan placed beneath a grooved weighted retractor inserted along the posterior vaginal wall. To this amount was added all blood squeezed from gauze sponges used during the operation (not more than one or two sponges were used in any of the caudal cases), and the total was measured. Clots removed from the uterus were separated from the products of conception and added to the amount measured. An estimated additional amount was added to the measured volume in each case in lieu of the blood that might have been lost on sponges, instruments, or in the process of collection.

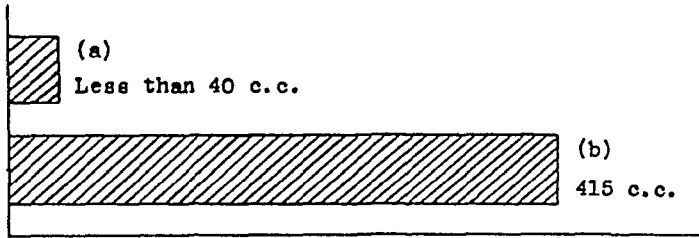


Fig. 1.—Comparison of average blood loss in curettage for abortion under (a) continuous caudal analgesia, (b) general anesthesia.

The blood pressure changes in this series of cases were not of appreciable significance. In only eight cases was there a systolic pressure fall of 20 mm. Hg. This blood pressure drop was transient, and no untoward symptoms were observed. In the remaining fourteen cases the blood pressure showed no significant deviation from the preinduction readings.

The postoperative course in all of the patients in this series was smooth and uneventful. The patients exhibited no febrile reaction, no blood pressure fall, no vomiting or abdominal distention, no urinary retention, no phlebitis, and postoperative discharge in no case was profuse. All patients were able to eat and drink immediately following the operation. The postoperative convalescence and return to normal activity is hastened, due in part to the absence of general anesthesia and certainly to the lack of significant blood loss at the time of curettage.

Summary

1. In an attempt to decrease blood loss at the time of therapeutic abortion and curettage for incomplete abortion we have used continuous caudal analgesia as an anesthetic method.

2. This technique maintains tonicity of the uterine muscle and at the same time provides analgesia of the perineum, vagina, and in the cervical and fundal portions of the uterus.

3. In 22 consecutive cases average blood loss was less than 40 c.c. per patient, varying from less than 5 c.c. to 125 c.c. Seventeen of the patients lost 50 c.c. or less.

4. There were no anesthetic, operative or postoperative complications.

5. Postoperative convalescence and return to normal activity of the patient is hastened.

References

1. Taussig, F. J.: *Abortion, Spontaneous and Induced*, St. Louis, 1936, The C. V. Mosby Co.
2. Petersen, E.: *Acta obst. et gynec. Scandinav.* 17: 449, 1937.
3. Hingson, R. A., and Edwards, W. B.: *Am. J. Surg.* 57: 459, 1942.

CLINICAL EXPERIENCE WITH A NEW SYNTHETIC ERGONOVINE-LIKE SUBSTANCE

JOHN E. TRITSCH, M.D., AND EDWARD SCHNEIDER, M.D., NEW YORK, N. Y.

(From the Department of Obstetrics and Gynecology of Metropolitan Hospital)

THE problem of the influence of oxytocic substances upon postpartum bleeding has long been a topic for discussion. Many have believed these drugs of little or no value due to several factors, among which have been the obvious uselessness of the drug in lacerations and the undependability of many of the various earlier preparations of ergot. Since the advent of ergonovine, however, greater numbers of obstetricians feel more confident that this drug has been of benefit, especially when given by the intravenous route.

By far the greater part of the ergot used in the United States is obtained from foreign sources, notably Russia and Spain, and it is entirely possible that, under certain conditions, such as war, drought, or blight, the natural ergot would not be obtainable in the necessary quantities. As a consequence, the development of a synthesized ergonovine-like substance would be an obvious advantage, for this reason as well as from the standpoint of permitting more accurate standardization.

It might be well to review briefly some salient points in the history of the development of the ergot alkaloids: In 1875, Tanret¹ obtained a crystalline ergotinine from ergot, but this alkaloid was only slightly active and possessed little or no pharmacologic or therapeutic significance. In 1906, Barger and Carr,² almost simultaneously with Kraft,³ discovered ergotoxine in amorphous form. Ergotoxine has been recently crystallized and is isomeric with ergotinine, according to Stoll.⁴ In 1920, Stoll isolated two new isomeric alkaloids, ergotamine and ergotaminine, from ergot, and in 1925 Stoeckel⁵ at the Gynecological Congress in Vienna called attention to the regular and constant effect of ergotamine as a uterine styptic.

In 1935, four different investigators reported a new aqueous ergot alkaloid, since assigned the name ergonovine by the Council on Pharmacy and Chemistry. Dudley and Moir⁶ called this ergometrine; Kharasch and Legault,⁷ ergotocin; Thompson,⁸ ergostetrine; and Stoll and Burckhardt,⁹ ergobasine. Recently, Stoll and Hofmann¹⁰ have synthesized, among other derivatives, d-lysergic acid d l hydroxybutyl-amide 2 also known as methyl-ergobasine tartrate or Methergine.*

Chemistry and Pharmacology

The general formula of Methergine may be compared with that of ergonovine:



R† represents lysergic acid molecule.

Methergine has been found comparable in utero-activity to ergonovine on isolated uterine strips of both rabbit and guinea pig. It does not reverse the adrenalin response on isolated rabbit uteri as does ergotamine. The re-

*Methergine was supplied by the Sandoz Chemical Works, Inc.

laxing action on the isolated guinea pig jejunum indicates slight adrenergic effect. It has shown no effect on the isolated virgin dog and rat uteri.¹¹

Clinically, in 200 cases of human administration, we have observed no toxic effects.

Physiology of Placental Separation

New theories have been advanced concerning the mechanism of the third stage of labor which provide a basis for the more modern application of oxytocic drugs in this stage.

Frankl originally believed that when the child was born, blood rushed into the placental site (a "*hyperemia ex vacuo*" mechanism), there was rhexis and blood extravasation in the decidua spongiosa, and a retroplacental hematoma was formed. With uterine contractions, this hematoma was driven as a fluid wedge between the layers of the decidua serotina, and the placenta was separated off.¹²

In the monkey, Danforth, Graham, and Ivy¹³ observed almost complete separation of the placenta at the end of the second stage. Similar claim is made for the human by Leff¹⁴ who states that the placenta separates immediately as the baby leaves the uterus. Usually, with the first uterine contraction there is marked diminution in the size of the placental site. The placenta shrinks somewhat, but not enough to compare to the placental site, and separation is inevitable.

Brandt¹⁵ has proposed that "as the child is being expelled, in a normal labor, the size of the uterus diminishes partly as a result of muscular tone and partly due to uterine muscle contraction. As a result of this change, the veins in the muscle layer of the uterus are compressed so that maternal blood in the placenta cannot escape from the uterus. At the same time, the reduction in size of the uterine cavity has squeezed the placenta so that the blood in the intervillous spaces is forced into the veins of the decidua. We therefore have a layer of overdistended veins in the decidua spongiosa, lying between a firmly contracted uterine wall and a more or less solidly compressed placenta. As a result of this viselike compression, the congested venous sinuses burst and the extravasated blood under tension causes tearing of the very fine septa of the spongiosa, thereby detaching the placenta from its uterine site.

"For this normal mechanism to occur . . . contracted uterine wall and compressed compact placenta must be present. If either of these is absent, separation does not follow a normal course. If the uterus does not contract as the child is being born, then separation does not occur until an afterpain has set in, causing reduction in the size of the uterine cavity as well as contraction of the muscular wall of the uterus. On the other hand, if the placenta is thinned out and covers an area much larger than normal, there does not develop the usual counterresisting mass of compressed compact placenta; hence separation is delayed.

"As the separated placenta is detached from its uterine site, it folds on itself, but is held in the uterine cavity because of the firm attachment of the membranes. If the uterine contraction . . . is strong . . . the placenta may be expelled into the lower uterine segment and upper vagina. . . . When this occurs, the retroplacental hematoma does not form and could have no function."

Third Stage Technique

It is the purpose of oxytocic drugs given before the placenta is separated to induce the strong contraction of the uterus which results in the mechanism of the third stage described above. The preparation which we have used in our experiment has been used in very few cases by other observers^{16, 17} who have "estimated" and not measured the blood loss in each case. We wish to present a preliminary report of our experience with Methergine in 200 cases.

In 1937 one of us¹⁸ suggested that the administration of Basergin given immediately at the end of the second stage definitely shortened the third stage of labor and decidedly decreased postpartum bleeding. Subsequently, Davin,¹⁹ in a larger series, made a similar recommendation with similar results.

In 100 cases, 1 c.c. of Methergine, containing 0.2 mg. per cubic centimeter, was given intramuscularly immediately following delivery of the placenta. In the other 100 cases, the same preparation and dose was given intravenously immediately following birth of the child and before the placenta was delivered. In both groups, the blood was measured as pre-

placental, placental, and for thirty minutes after birth of the placenta. No deductions have been made for bleeding from lacerations or episiotomies in the routine case.

In the cases handled by the intramuscular method, a modified Credé maneuver was used to deliver the placenta. In the cases handled by the intravenous method, the placenta was delivered in the following manner: The umbilical cord was clamped close to the vulva. The uterus was palpated to insure a firm contraction. The clamp at the vulva was then held firmly in one hand while the fingertips of the other hand were inserted abdominally between the fundus and the symphysis pubis. Upon elevation of the fundus toward the sternum, failure of the cord to retract into the vagina was taken as evidence of separation of the placenta and continued elevation of the fundus associated with minimal traction on the cord resulted in delivery of the placenta. Where the cord retracted into the vagina, the placenta was assumed to be attached or incarcerated, and no attempt was made to deliver the placenta until later repetition of the maneuver revealed its freedom.¹⁵

In all cases, the blood loss was measured accurately in the following manner: A sterile metal pan was placed beneath the patients' buttocks. Extending from this pan was a trough emptying into a graduated container which was at all times under the direct vision of the accoucheur. This container was on a movable arm which could be maneuvered by the operator's knee in order to avoid inclusion of amniotic fluid and other possible diluents. (Figs. 1 and 2.)

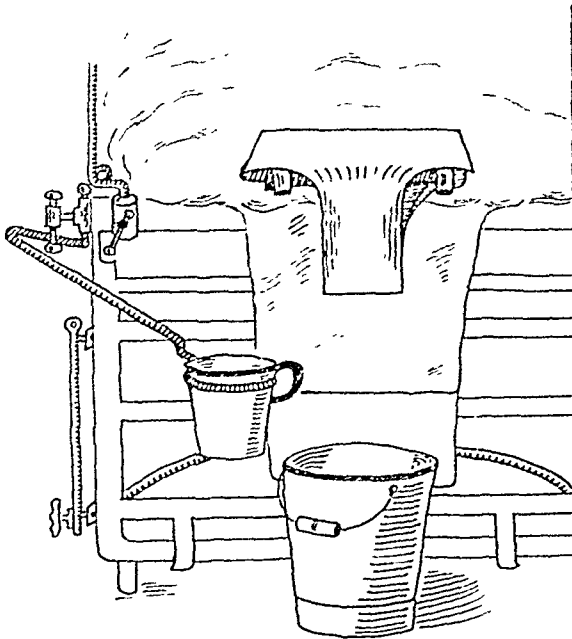


Fig. 1.

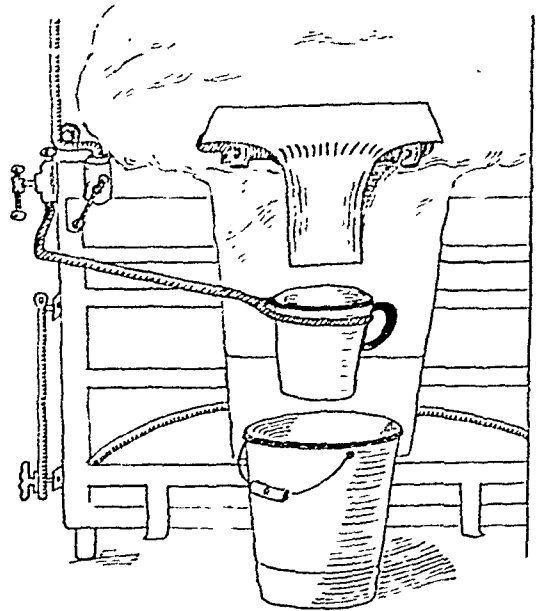


Fig. 2.

Analysis of Results

In both the intravenous and intramuscular groups there were 30 primigravidas and 70 multigravidas.

In the intravenous group, operative obstetrics was performed in 15 primigravidas and 5 multigravidas for an incidence of 20 per cent. In the intramuscular group, 9 primigravidas and 3 multigravidas, an incidence of 12 per cent, required intervention.

The average blood loss with the intravenous technique was a gross of 113.24 c.c. and a net of 90.35 c.c. The average blood loss for the intramuscular group was 168.07 c.c. gross and 159.68 c.c. net. In the intravenous group, the primigravidas averaged 116.03 c.c. gross, and 94.13 c.c. net, while the multigravidas averaged 112.05 c.c. gross and 87.22 c.c. net. In the intramuscular group, the primigravidas averaged 173.0 c.c. gross and net, while the multigravidas averaged 165.96 c.c. gross and 153.86 c.c. net. These corrections will be explained below.

The largest blood loss occurred in one case (No. 5) of the group receiving Methergine intramuscularly. However, in this instance, other factors which could not be controlled by Methergine or any oxytocic were felt to be responsible and will be dealt with in greater detail. The smallest blood loss occurred in the group receiving Methergine intravenously; in many of these cases the blood loss was so slight that it could not be measured.

The third stage averaged 7.68 minutes in the intravenous group and 10.38 minutes in the intramuscular group. No attempt was made to deliver the placenta as soon as it was separated. In most cases, the baby was attended and then the third stage was terminated. In spite of this, the third stage in both groups of cases was of shorter duration than the average time quoted as normal in textbooks.

Manual removal of the placenta was required three times in the intravenous group and not at all in the intramuscular group. In one of these three cases, the procedure was elective after 74 minutes in a nonbleeding third stage. The placenta here was found completely attached. The other two cases are included in the five cases for which we have offered correction in our results. These may now be explained:

CASE 1.—A. O. Delivered by low forceps and episiotomy of a 9-pound 8½-ounce male child. Methergine, 1 c.c., given intravenously. As soon as the baby was born, the episiotomy bled 600 c.c. from a large severed vessel despite immediate repair. Third stage completed with no additional blood loss.

CASE 2.—M. R. Delivered spontaneously of an 8-pound 9½-ounce baby. Given Methergine 1 c.c. intravenously. After 1½ hours with no sign of bleeding or separation, a completely attached placenta was manually removed. Due to deep anesthesia and resultant atonicity of the uterus, patient bled 1,000 c.c. and had to be packed. Past history revealed manual removal of the placenta with postpartum hemorrhage in her previous two deliveries.

CASE 3.—C. G. A 5-pound 13-ounce female child delivered from right occipitoposterior by manual rotation and extraction with DeLee forceps. Methergine, 1 c.c., given intravenously. After one hour with no sign of bleeding or separation, a completely attached placenta was manually removed with 500 c.c. blood loss.

CASE 4.—J. M. Delivered a 6-pound 9-ounce male child spontaneously. Given Methergine, 1 c.c., intravenously. Third stage terminated immediately. Due to moderate bleeding, inspection was made. A cervical laceration and clitoroidal laceration were both repaired. Blood loss totaled 500 c.c., practically all of which came from the lacerations.

CASE 5.—C. M. Spontaneously delivered an 8-pound 12-ounce child. Placenta delivered in six minutes without administration of oxytocic drugs. Sudden hemorrhage of 1,150 c.c. halted by Methergine, 1 c.c. intravenously and 1 c.c. intramuscularly with uterine massage.

Blood loss of 500 c.c. or more was found only in the above five cases for an incidence of 2½ per cent in these 200 cases.

Comparison of our blood loss with reports in the literature may be made by referring to Tables I and II.

TABLE I. COMPARISON OF BLOOD LOSSES REPORTED BY TWENTY DIFFERENT OBSERVERS*

	c.c.		c.c.
Tarnier	600.0	Brandt	195.0
Ahlfeld	505.1	Vaux et al.	192.62 (Inhalation)
DeLee	500.0	Jess	187.8
Williams	343.7	Calkins	179.0
Plass	317.0	Ryder	177.0
Tucker	300.0	Left	171.75
Fortin	275.0	<i>Present series</i>	168.07 (Gross) (Intramuscularly)
Pastore	271.3	<i>Present series</i>	113.24 (Gross) (Intravenous)
Calkins	222.0	Arnell	111.0
Scott	198.7	Vaux et al.	110.75 (Caudal)
		Adair et al.	100.0

*Many of these reports were estimations and not accurate measurements.

TABLE II. INCIDENCE OF POSTPARTUM HEMORRHAGE (501 TO 600 c.c. OR MORE)

	%		%
Adair et al.	13.7	Urner	3.4
Williams	13.0	Vaux and Mitchell	2.8
Fortin	7.4	Calkins	2.5
Pastore	7.1	<i>Present series</i>	2.5 (Gross)
Pastore	6.4	Brandt	1.25
Peckham and Kuder	6.14	Polak	0.30
Tucker and Benaron	4.2	Vaux and Mitchell	0.00 (Caudal)

Comments

1. Methergine, a synthetic ergonovine-like substance, appeared to be nontoxic administered intramuscularly in 100 cases and intravenously in 100 cases.

2. This drug appeared to reduce postpartum blood loss by both methods of administration as compared to other available statistics.

3. When given intravenously immediately after the birth of the infant, the drug produced definitely less blood loss than when given intramuscularly immediately following placental delivery.

4. By the intravenous route, immediately following delivery of the child, the placental delivery is accelerated by about three minutes.

5. Incarceration occurred in the intravenous group in 3 per cent of the cases, but placental removal was easily accomplished under general anesthesia.

Conclusion

We are of the opinion, from this preliminary series of cases, that Methergine is a nontoxic and efficient oxytocic drug.

References

1. Tanret, C.: *Compt. rend. Soc. de biol.* 81: 896, 1875; *Ibid.* 86: 888, 1878.
2. Barger, G., and Carr, F. H.: *Chem. News* 94: 89, 1906.
3. Kraft, F.: *Arch. Pharm.* 244: 336, 1906.
4. Stoll, A.: *Schweiz. med. Wehnschr.* 65: 1077, 1935.
5. Stoeckel, F.: *Arch. f. Gynäk.* 125: 1, 1925.
6. Dudley, H. W., and Moir, C.: *Brit. M. J.* 1: 520, 1935.
7. Kharasch, M., and Legault, R. R.: *J. Am. Chem. Soc.* 57: 956, 1935.
8. Thompson, M. R.: *J. Am. Pharm. A.* 24: 185, 1935.
9. Stoll, A., and Burekhardt, E.: *Compt. rend. Soc. de biol.* 200: 1680, 1935.
10. Stoll, A., and Hofmann, A.: *U. S. Patents* Nos. 2, 265, 207 and 2, 265, 217.
11. Kirchhof, A. C., Racely, C. A., Wilson, W. N., and David, N. A.: *West. J. Surg.* 52: 197, 1944.
12. DeLee, J. B., and Greenhill, J. P.: *Principles and Practice of Obstetrics*, ed. 8, Philadelphia and London, 1943, W. B. Saunders Co.
13. Danforth, D. N., Graham, R. J., and Ivy, S. C.: *Surg., Gynec. & Obst.* 74: 188, 1942.
14. Leff, M.: *AM. J. OBST. & GYNEC.* 18: 868, 1929; *Surg., Gynec. & Obst.* 68: 224, 1939.
15. Brandt, M. L.: *AM. J. OBST. & GYNEC.* 25: 662, 1933.
16. Roberts, P. C.: *West. J. Surg.* 52: 380, 1944.
17. Tollefson, D. G.: *West. J. Surg.* 52: 383, 1944.
18. Tritsch, J. E., and Behm, K. H.: *AM. J. OBST. & GYNEC.* 34: 676, 1937.
19. Davin, E. J., and Morris, T. N.: *M. Ann. District of Columbia* 9: 1, 1940.
20. Vaux, N. W., and Mitchell, R. M.: *J. A. M. A.* 124: 549, 1944.

DYSTOCIA DUE TO THE SHOULDERS

CHARLES G. BARNUM, M.D., GROTON, CONN.

(From the Obstetric Service of the Lawrence and Memorial Associated Hospitals of New London, Conn.)

DYSTOCIA due to the shoulders occasionally presents a serious problem. This may be due to one or a combination of several factors; with an over-size baby, the shoulders are large in proportion to the head and the anterior shoulder may impinge upon the anterior arch of the pelvis in such a manner as to offer a serious obstacle to delivery. This event may occur unexpectedly, when a large baby is being delivered through a slightly contracted pelvis through which a moderate-sized baby had previously been successfully and easily delivered. The use of analgesics and anesthetics contribute to the difficulty of the situation because they practically eliminate the possibility of co-operative assistance on the part of the patient and minimize the effectiveness of the natural forces.

Faced with a situation of this sort, the writer extemporized the following procedure: With adequate anesthesia the fetal body was allowed to rise into the mother's abdomen as far as it would. The operator's hand was passed in posteriorly to find the posterior arm, and, failing to flex the elbow, the operator's hand was advanced till the fetal wrist could be released from its position across the posterior border of the pelvic inlet. The fetal elbow was then flexed and the hand gradually swept down over the anterior chest. At this point in the procedure the posterior shoulder was out, but the anterior shoulder was still engaged against the symphysis.

To release this anterior shoulder the fetus was rotated approximately 180 degrees (with the help of an assistant) so that the shoulder which was out came into a position just outside the symphysis. This maneuver entirely unlocked the obstruction and the remainder of the delivery was readily completed.

Subsequently the fore part of this procedure was found very nicely presented by DeLee in his textbook, *The Principles and Practice of Obstetrics*, and a similar presentation appears in Titus' work, *The Management of Obstetric Difficulties*. Both of them have stated that after delivery of the posterior shoulder the remainder of the delivery is readily accomplished. This does not appear always to be the case and DeLee's illustration shows the operator's hand making suprapubic pressure to force the anterior shoulder under the symphysis, which might subject the fetal thorax to severe compression. In such a case the lungs are not aerated and are relatively incompressible so that the pressure may be transmitted to the heart, preventing the filling of its chambers, stalling the circulation, and leading very soon to permanent cardiac arrest. The maneuver of rolling the baby over on its longitudinal axis and unlocking the obstruction avoids compression of the thorax, facilitates the delivery, and should prove a useful addition to the procedure.

Since first extemporizing this procedure, several years ago, the writer has had several occasions to resort to the maneuver when the commoner methods failed to complete the delivery.

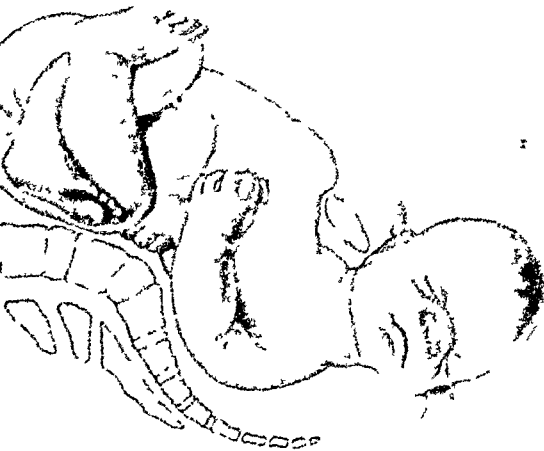


Fig. 1.—Impaction of the anterior shoulder against the symphysis in the case of an oversize fetus, preventing delivery without damage unless the impaction is decomposed.

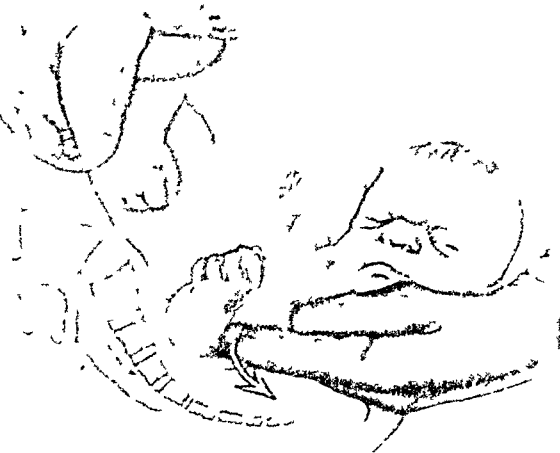


Fig. 2.—Pressure with the index finger at the bend of the elbow flexes the arm and brings the wrist within reach. Often the wrist is so pinned against the posterior border of the pelvic inlet by the fetal trunk that the operator must carry his hand higher and release the wrist directly.



Fig. 3.—The fetal forearm is swept down over the front of the fetal chest and the hand brought out.

Fig. 4.—The posterior fetal hand and arm having been brought out, the posterior shoulder rides over the perineum which is crowded back by the arm as it is allowed to hang down. In some cases delivery may follow easily; in others, the impaction of the anterior shoulder against the symphysis is a serious obstacle.

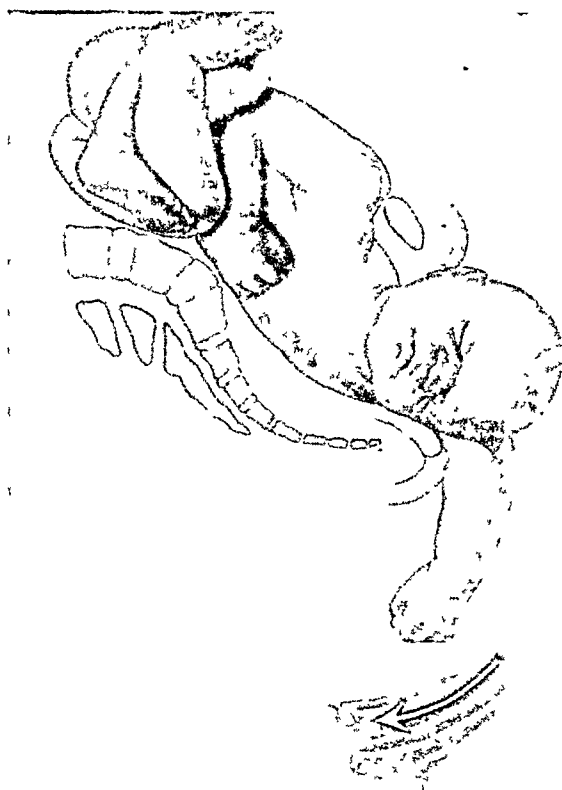


Fig. 5.—To disengage the anterior shoulder, the occiput is grasped with one hand and the posterior shoulder with the other, while an assistant pushes the fetal back over the midline to the other side of the mother's abdomen as the posterior shoulder is brought to the front.



Fig. 6.—Completion of the rotation of the fetus on its long axis with complete release of the impaction of the shoulders.



In these cases delivery was accomplished entirely without injury to mother or baby. Rolling the fetus over, carrying the fetal back over the mid-line of the mother's abdomen to the side toward which the fetus originally faced, thus completely releasing the anterior shoulder, is the only feature not previously described, to the knowledge of the writer.

SICKLE-CELL ANEMIA COMPLICATED BY PREGNANCY

MARY SPIVACK, M.D., M.S., CHICAGO, ILL.

(From the Salvation Army Booth Memorial Hospital)

THE number of published cases of sickle-cell anemia complicated by pregnancy is so scarce that the description of another may be justified.

From the literature the author was impressed with the fact that in several cases the nature of the anemia or even the anemia itself, in spite of the prenatal care, were not diagnosed until after the patient's admission to the hospital either because of the onset of labor or of an intercurrent infectious disease. Moreover, in a few unfortunate cases the correct diagnosis was made at the post-mortem table only. Inasmuch as the foreknowledge of the existence of this serious ailment may alter the prenatal care and thereby improve the immediate prognosis, greater awareness of this condition and its means of detection may be of considerable practical importance. The author had an opportunity of studying a case of sickle-cell anemia long before term and at close range.

L. S., a 35-year-old nulliparous Negro woman, presented herself with the complaints of amenorrhea of about seven months' duration. The last menstrual period occurred on Oct. 15, 1943. Presently she complained of shortness of breath on slightest exertion, fatigue, and mild pains in the muscles of the thighs, noticeable especially upon locomotion. Her past history revealed that besides the usual childhood diseases such as measles, mumps, chicken pox, and whooping cough, the patient had had typhoid fever at the age of 12 years. When about 14 years old, an anemia of undetermined etiology was diagnosed. In her early teens the patient underwent a tonsillectomy and in her adult life (1938) an appendectomy from which she made an uneventful recovery. Menstruation began at the age of 13 years and was uneventful until the year preceding pregnancy when the intervals between the periods lengthened to six to seven weeks, instead of the usual twenty-eight days. The flow lasted three days and was scanty as usual.

The family history was irrelevant to her present condition. The patient was one of six children. Neither of the parents and none of the siblings had suffered from anemia of any kind. The father was dead, the mother is hypertensive and still living.

As long as the patient could remember she had been troubled with intermittent muscular pains of various intensity. At times the pain was so severe that she had to be confined to bed and strong sedatives were needed to alleviate it. Several groups of muscles usually were involved, namely, those of the thighs, hands, wrists, neck, and abdomen. During these attacks some elevation of temperature occurred, and as high as 103° F. was encountered upon a few occasions. In her early childhood these attacks were considered "growing pains," even when, at the age of 14 years, an associated anemia was discovered. The nature of the anemia was not understood then, but its severity and lack of response to medical management necessitated a blood transfusion. At this period of her life the patient's health was impaired to such an extent that her schooling had to be interrupted for a whole year. The following few years the patient was well enough not only to resume her general education but even to take up nurse's training and to practice her profession successfully. After several years of satisfactory health, the patient, at the age of 20 years, had one of her attacks of muscular pains and the sickle-cell nature of her anemia was diagnosed for the first time. She was treated medically off and on, and during the following ten years the attacks of muscular

pain of various severity intermingled with periods of comparatively fair health. In 1938 the patient was stricken with pneumonia. A week later she developed a typical attack of muscular pain, fever of 102° F., nausea and vomiting. The blood picture at this time showed a red count of 3,000,000 with a leucocyte count of 27,000. The patient under medical treatment improved subjectively, but not objectively, the blood picture remaining unchanged; a few months later the red blood count fell even below 2,000,000 per cubic millimeter. Since 1938 the patient had had, on the average, one or two exacerbations yearly, during which time the sickle-cell nature of her anemia was confirmed on several occasions. In February, 1944, her red blood count fell to the low level of 1,500,000 per cubic millimeter. She needed three blood transfusions in one week to restore her health. At this time a pregnancy of about three and one-half to four months was detected. The onset of the pregnancy was uneventful in every other respect; no vomiting or nausea accompanied it. The presence of albumen was a constant finding in the urine for some time prior to and throughout the pregnancy. Upon admission to the hospital the patient at thirty-two weeks' gestation weighed 109 pounds. She was found to be of small stature (4 feet, $11\frac{1}{2}$ inches) and of slender build. She appeared undernourished and her extremities were especially thin. Her heart was enlarged to the left; the apex beat was felt at the sixth costal interspace. A loud systolic murmur was heard at the apex and base.

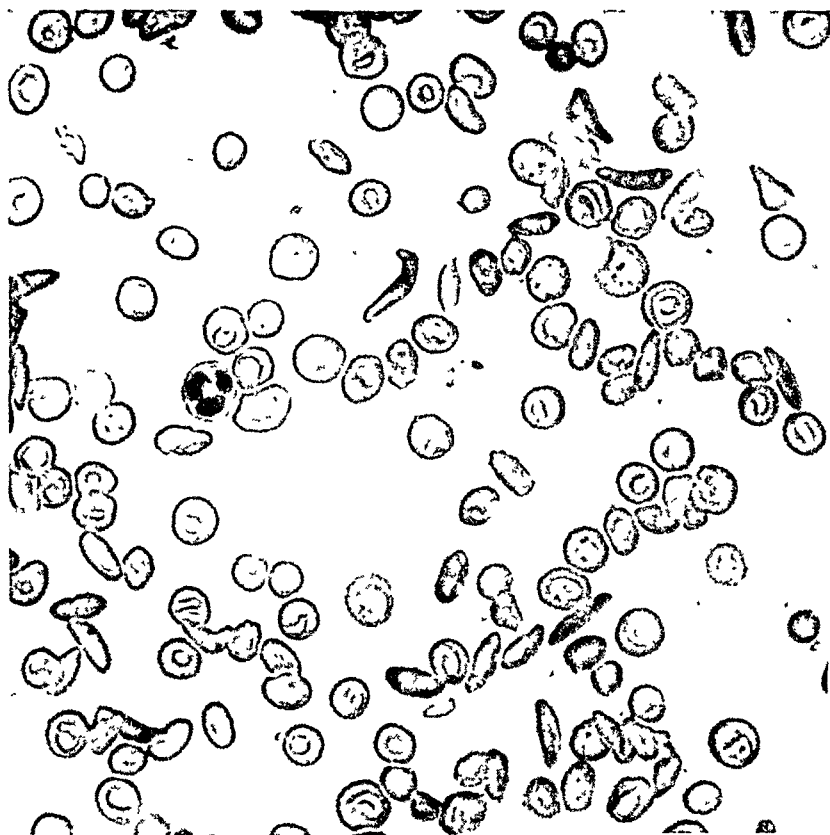


Fig. 1.—A stained preparation of peripheral blood ($\times 540$). Note the hyperchromatic elongated and sickle-shaped cells.

A few crepitant râles were heard in the lower portions of both lungs posteriorly. The abdomen was tense due to considerable meteorism, and its wall showed a wide right rectus scar. The spleen and liver were not palpable then. The fetus was in cephalic presentation, and its heart tones were of good quality. The pelvic measurements revealed a generally contracted and funnel-shaped pelvis. Interspinous diameter measured 24 cm., intercrystal 25 cm., intertrochanteric 26 cm., Baudelocque 17.5 cm., and the diagonal conjugate 11 cm. The conjugata vera was estimated at 9 cm., the pubic arch at about 80 degrees, and the biischial measured $7\frac{1}{2}$ cm. The vagina was short and narrow, the vulva infantile. The blood pressure upon first examination read 130/90 and the pulse 96. Both sclera showed yellow-brown patches. The laboratory findings were as follows:

Red cell count	3,050,000
White cell count	8,200
Hemoglobin	54 per cent

There were 15 to 20 per cent of sickle cells in the dry smear and 80 per cent in a twenty-four-hour moist preparation. Anisocytosis and polychromasia were detected. Normoblasts were seen in the amount of 97 cells per 100 white blood cells. Howell-Jolly bodies and punctate basophilia were observed. Reticuloocytes were increased up to 15 per cent. The platelets were approximately within normal limits, amounting to 210,000 per cubic millimeter.

The differential count of white cells revealed 82 per cent polymorphonuclear cells, of which 8 per cent were stabs and 74 per cent segmented forms. Besides these, 10 per cent were small lymphocytes, 3 per cent large lymphocytes, and 5 per cent monocytes. The bleeding and coagulation time were well within normal range, namely two and one-half and four minutes, respectively. The icteric index of the blood was increased to 29 per cent. The patient was serologically negative and free from Neisserian infection. The blood belonged to group A and contained the Rh factor. A urinalysis revealed the presence of albumen in the amount of 2 Gm. per thousand. Occasional hyaline casts were found microscopically. Blood chemistry showed a nonprotein nitrogen of 27 mg., and 4.3 mg. of uric acid per 100 c.c. of blood.

The patient was hospitalized during most of her stay at the Salvation Army Home. During this time she complained frequently of mild pains in different muscular groups, mostly in those of the extremities. She ran a slight afternoon temperature, ranging from 99 to 100° F.; the most frequent temperature, however, was 99° F.

Upon three occasions the muscular pain was so severe that only morphine sulfate in $\frac{1}{4}$ grain doses was able to bring her relief. The patient was placed on a high-protein salt-restricted diet. Iron sulfate, 5 grains three times a day, vitamin B complex three times a day, and vitamin C in 50 mg. doses were the oral medication of this time. Despite the treatment and considerable amount of bed rest (the patient was allowed to be out of bed daily for short periods of time), three weeks later the red count fell to 2,400,000 and the hemoglobin remained practically unchanged (55 per cent). On June 27 the patient received 500 c.c. of compatible citrated blood from a donor of the same group and Rh positive. No untoward reactions occurred. A week later the red count rose to 3,400,000 and the hemoglobin to 58 per cent. The patient improved subjectively; she complained of less fatigue and a diminution in muscular pain was noted. On July 7 another blood transfusion was given from a universal donor, the blood being cross-matched. At the conclusion of the transfusion, the patient developed an attack of severe pain in the muscles of the neck and in the epigastrium. Morphine alone was able to bring comfort. The temperature remained normal; chills were not present and the urinary output not diminished. This attack of headache and muscular pain was considered the usual manifestation of her disease and not a reaction from the blood transfusion. After this transfusion the patient improved again, the weakness was less complained of, and the muscular discomfort less pronounced.

On July 11, one week before the expected date, the patient fell into labor. The fetus was in right occipitoposterior presentation. The heart tones were regular, the rate fluctuating between 132 to 140. The head was at the level of the spine, the pains were strong and frequent, but the progress slow. Her blood pressure at the onset of labor was 140/92 and rose to 150/100 at the end of the first stage, which lasted thirty hours. Morphine sulfate, $\frac{1}{4}$ grain, procured the much-needed rest, and after a second stage of almost three hours the head was still in a posterior position. A midforceps was done after a preliminary left mediolateral episiotomy, and a 5-pound 5½-ounce male infant was extracted with difficulty. The infant was born in good condition and continued to do well throughout its neonatal period. At the age of 3 weeks he showed a red count of 5,310,000 cells, hemoglobin 80 per cent, and a sickle-cell trait. The mother made a good recovery. There was no morbidity according to the accepted standards. The highest temperature was 100.2° F. which occurred once only during the first twenty-four hours following delivery. The unusual feature of the puerperal period was the considerable intestinal distention and acute dilatation of the stomach, occurring on the second day postpartum. Gastric lavage relieved the stomach distention, and prostigmine methylsulfate 1:2,000 given intramuscularly in conjunction with enemas combated the intestinal distention within the following twenty-four hours. Another notable feature of the puerperium was an extremely small amount of lochia, some days almost none. On the ninth day the patient was allowed out of bed. She felt well and continued to do so throughout the period of observation, which ceased at six weeks postpartum. Three weeks after childbirth the blood count revealed 2,900,000 red cells per cubic millimeter and 50 per cent hemoglobin. Anisocytosis and a moderate number of sickle cells were present. The icteric index fell to 16 per cent. Repeated urinalyses throughout her postnatal period continued to show the presence

of 3 plus albumen and occasional hyaline casts. Upon the final examination her general health was found to be better than at any other time since her pregnancy started. The pelvic organs involuted well. The episiotomy healed very well, and the pelvic floor was good. The heart showed the same findings as upon admission. The spleen was not palpable but the liver was felt 3 fingerbreadths below the right costal margin. It is likely that the enlarged liver was not palpable during pregnancy due to tenseness of the abdomen. The patient left the hospital for her home state in good condition. She has been heard from since as being employed and enjoying fair health (first week of January, 1945).

Discussion

Sickle-cell anemia since its description in 1910 by Herriek is a well-known clinical entity. According to the literature it is a familial and hereditary disease, the sickle-cell trait being transmitted according to the Mendelian law as a dominant factor. The clinical picture is so characteristic that once the condition is suspected it is easily diagnosed. If one keeps in mind the salient features of this ailment, such as attacks of muscular and joint pain, weakness, elevation of temperature in the presence of anemia, one is likely to arrive at a correct diagnosis. Of late, proper emphasis has been placed upon the frequency of secondary anemias, occurring in pregnancies, and a routine blood count is advocated for their detection. Should an anemia thus found be associated with a history of attacks of muscular and joint pains, then a suspicion of sickle-cell anemia should arise, and the diagnosis either be confirmed or refuted by complete blood study of fixed and moist preparations. This is especially true when the patient is a Negro because of the susceptibility of this race to the ailment.

The association of sickle-cell anemia with pregnancy is not frequently met with; only 17 cases have been described thus far. Kobak and associates (1941) analyzed and summarized the literature upon this subject. In the series collected by them from the literature, the average age of those afflicted with this blood dyscrasia is 22.4 years, the oldest patient being 30 years old. It is a known fact that this condition has a predilection for the young; its incidence progressively decreases as the age increases. No case has been recorded in a patient over 30 years of age (Sydenstricker, 1930). It is believed by some (Sodeman and Burch, 1937) that fertility is impaired in those suffering from this type of anemia. According to several observers pregnancy exercises an unfavorable course upon the disease and the mortality among the patients is high. About 33 per cent of the reported pregnant cases died during pregnancy, labor, or puerperium (Kobak). No specific treatment is known to exist; the response to medication is unsatisfactory. Blood transfusions improve the patient's condition temporarily at least. Patients are very susceptible to infectious diseases to which they finally succumb. A few patients were described who died not from infection but during an abdominal crisis, the cause of which was not definitely known, but which was probably due to infarction occurring in some abdominal viscus (Yater and Mollari, 1931). As far as the author can judge from the literature, the 35-year-old patient here described is the only one among the sufferers of sickle-cell anemia to reach this age; the oldest among the previous reported cases have not exceeded the age of 30 years. It is likely also that the duration of the anemia is the longest among those thus far described. It is definitely known that the sickle-cell nature of her anemia was diagnosed fifteen years ago, but it is probable that the anemia of her childhood was a manifestation of the same condition. In spite of the impaired general health, the hypomenorrhea and oligomenorrhea, the patient, an unmarried woman, readily conceived just a few weeks after sex relations were commenced and practiced in modera-

tion. Thus, seemingly, her fertility was not affected adversely, in contrast to the view of those who hold that such is the case with other patients. It appears from the study of this case that pregnancy does aggravate the condition of the patient's anemia. During the long span of her anemia, only in the beginning of the pregnancy did the red blood count reach its lowest ebb of 1,500,000 per cubic millimeter.

Unlike the majority of other patients with sickle-cell anemia, this one, fortunately, did not run a febrile puerperal course in spite of the prolonged labor and operative delivery. This, in part, is possibly due to the fact, as the author would like to believe, that the patient was well prepared for her ordeal by repeated blood transfusions, given not as an emergency measure during a crisis but prophylactically as part of the antenatal care and at the onset of labor.

Just as it is essential to treat medically the secondary anemias of pregnancy in order to build up the resistance of the patient and thus enable her to meet the exigencies of a difficult delivery or a postpartum hemorrhage, the occurrence of which cannot be foretold beforehand, so much more important, even imperative, is it to prepare the sickle-cell anemia patient for her ordeal with the only effective means at our disposal, namely, the supply of normal blood. True enough as expected, the blood transfusions do not cure the pregnant patient and do not alter the unfavorable prognosis. But if by administration of blood the patient can be carried through this difficult and potentially dangerous period of her life with greater safety, then the blood transfusions must be regarded as of paramount importance in the care of such patients.

Even though the success achieved is temporary and the inevitable outcome is only delayed, the obstetrician may consider his task well accomplished for the time being. Only further progress in the knowledge of this dyscrasia and its causes may render its treatment more specific and the prognosis more favorable.

I wish to express my gratitude to Dr. H. Sweeny of the Municipal Tuberculosis Sanitarium Laboratories for the various and numerous tests performed with unfailing courtesy by his technical staff of assistants. Without his cooperation the study of this case would have been impossible.

I am also greatly indebted to Dr. I. Davidsohn, the Director of the Laboratories of the Mount Sinai Hospital of Chicago, for his help in the study of the Rh factor of the patient and the compatibility of her blood with that of the prospective donors.

References

1. Herrick, J. B.: *Arch. Int. Med.* 6: 517, 1910.
2. Kobak, A. J., Stein, P. J., and Daro, A. F.: *AM. J. OBST. & GYNEC.* 41: 811, 1941.
3. Sydenstricker, V. P.: In *Christian's Oxford Medicine*, New York, 1930, Vol. II, Part III, Chap. XXIII, p. 849.
4. Sodeman, W. A., and Burch, G. E.: *New Orleans M. & S. J.* 90: 156, 1937.
5. Yater, W. M., and Mollari, M.: *J. A. M. A.* 96: 1671, 1931.

5040 PULASKI ROAD

CONGENITAL ABSENCE OF THE SACRUM AND COCCYX COMPLICATING PREGNANCY

CAPTAIN WILLIAM BERMAN, MEDICAL CORPS, UNITED STATES ARMY

(From the Station Hospital, Fort Riley, Kansas)

UNUSUAL pelvic abnormalities during pregnancy are important from the point of view of management during labor. These abnormalities have become more important in recent years with the more common usage of roentgen pelvimetry. Many unsuspected abnormalities have been discovered by this important method of examination, and this has undoubtedly reduced the incidence of so-called difficult labor. The use of the x-ray in borderline cases and in cases of unexpected bony abnormality is therefore of extreme benefit to the obstetrician. The following case presents a rare congenital abnormality of the pelvis in which there was a total absence of the sacrum and coccyx. This is visualized in the x-rays, Figs. 1 and 2. In addition to this bony abnormality, this case presents certain urologic complications as manifested by a total incontinence of urine due to a lack of sphincter control. The following case history is presented:

A 20-year-old white primipara was first seen in the prenatal clinic when she was approximately sixteen weeks pregnant. Her estimated date of confinement was Sept. 26, 1942. Her prenatal course and past history were relatively uneventful except for her skeletal development. She was aware of having a skeletal anomaly but was not aware of its extent. She also gave a history of being incontinent and partially involuntary, although she had some tone to her rectal sphincter muscles. She had been seen by numerous physicians and it was at one time suggested that she have a ureteral implantation into the large bowel for congenital incontinence. She refused this operation at the time. The patient stated that she used from six to eight dozen sanitary napkins daily and always wore baby rubber pants because of her bladder difficulty. Her family history was negative with reference to any etiological agent in the patient's condition. The patient was of short stature (5 feet 1 inch in height) with a broad (masculine) type of shoulder girdle. She had thick pectoral and deltoid muscles in comparison to those of the rest of her body. Her vertebral column was straight and terminated at the junction of the last lumbar vertebra and the pelvic girdle. There were two marked depressions at the site of the posterior superior spines of the ilium. There was almost a complete absence of the intergluteal fold, and the subcutaneous tissue and muscle formed a partially loose apron over what would normally be the sacrum. Although there was some tone to the rectal sphincter, there was no difficulty in inserting two fingers into the rectum without much discomfort to the patient. There was a moderate atrophy of the thigh muscles and a marked atrophy of the muscles of the leg and foot. The patient had a waddling gait, but there was no evidence of unsteadiness on walking. There was no loss of sensation to touch or temperature below the umbilicus, and there was no loss of motor function. X-ray of the pelvis at term showed a single fetus with the back to the left and the small parts to the right (Fig. 3). The head was above the pelvic inlet and ballotable on palpation above the brim of the pelvis. The head appeared to be full term in size. The pelvic inlet was asymmetrical and did not correspond to any of the pure types of pelvis described either by the Thoms or Caldwell-Moloy classification. It appeared cylindrical in appearance with the greatest diameter of the cylinder running anteroposteriorly. The head seemed to be too large for the pelvic inlet and could not be pushed into the inlet by manipulation over the brim of the pelvis. A diagnosis of relative cephalopelvic disproportion was made and it was deemed advisable to give the patient a test of labor. She was admitted to the hospital on Nov. 11, 1942, and the following day she was given 1 minim of pitocin. Following this injection she had hard contractions which came every four to six minutes and lasted forty to fifty seconds. The patient made no progress. Since she showed no other abnormalities with reference to the pregnancy itself, it was deemed advisable to continue with the test of labor. She had some contractions all through that night and the following day the contractions became more severe and more frequent. Still she made no progress and it was decided at this time to interfere.



Fig. 1.—Lateral view of the pelvic girdle showing the absence of the sacrum and coccyx. There is some sacralization of the last lumbar vertebra.

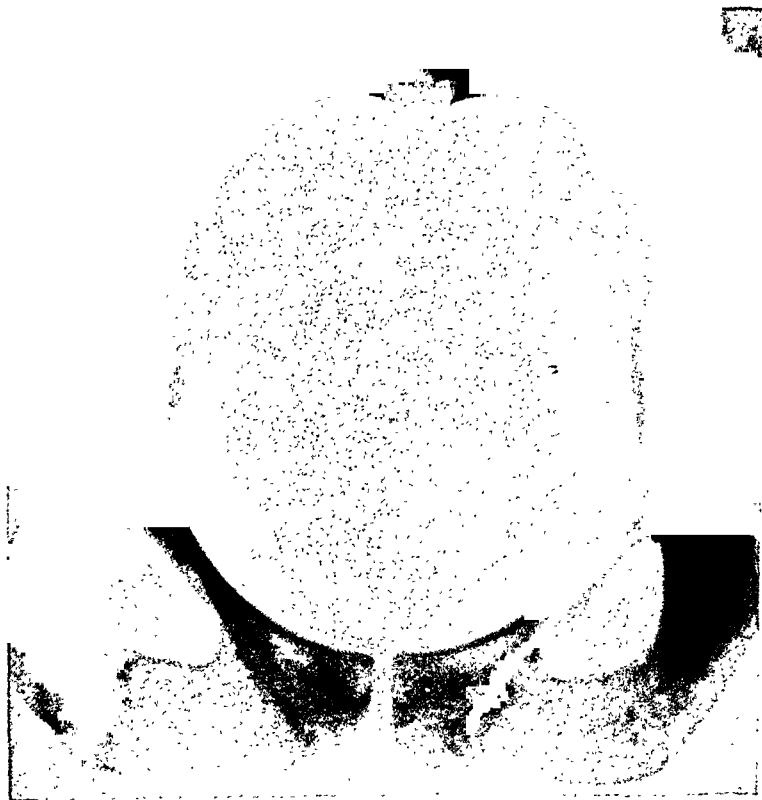


Fig. 2.—Anteroposterior view of the pelvis showing the absence of sacrum and coccyx.

Under spinal anesthesia a low classical cesarean section was done and a living infant was delivered that gave a spontaneous cry and respiration. The infant stopped breathing shortly thereafter and failed to respond after several attempts at resuscitation. Autopsy revealed that the baby had a congenital heart lesion and a complete atelectasis of all lobes of the lungs. X-ray of the baby's spine failed to reveal any abnormality of the bony structure. The patient had an uneventful postoperative course and was discharged from the hospital in good condition. Her urinary difficulty continued, however, and she was readmitted for surgical treatment of her incontinence. On Jan. 6, 1944, under general anesthesia, a combined vaginal and abdominal operation was done for relief of her incontinence. A cystocele repair was done and two portions of the sheath of the rectus abdominis muscles were brought under the bladder for support according to the method described by Aldridge.¹ There was no immediate relief from the procedure, but within a period of three months the patient experienced a desire to urinate which was something she had never enjoyed previously. However, she was still unable to hold her urine and would usually expel it spontaneously before reaching the lavatory. This has since improved somewhat but not to any great extent. This patient is now again pregnant and time will tell what the effects will be on the operation for urinary incontinence. At the present writing no change has occurred over that of her prepregnancy status.



Fig. 3.—Anteroposterior view of the lower abdomen and pelvis showing configuration of the pelvic inlet and the fetal head riding above the inlet.

This is an extremely rare anomaly of the pelvis. Aldridge¹ reports in his article on urinary stress incontinence that procedure similar to this was used on a girl operated upon by Price.² The latter's patient was a young Chinese girl who came for help because of incontinence of urine and feces due to a lack of sphincter innervation. She was operated on at 16 years of age. She had two operations with good results. Although this girl had incontinence of urine primarily, she also had a congenital absence of the sacrum and coccyx, which undoubtedly accounts for this incontinence. Price gives no reference to any other cases similar to this abnormality.

In the case here presented the uterus responded to labor like any other normal uterus. Contractions were regular and of sufficient strength to require the use of some analgesia. The cervix dilated but there was no descent of the head. It was felt that a test of labor would indicate whether the head would

pass the widest diameter of the pelvic inlet, but due to the absolute disproportion between the fetal head and the pelvic inlet, there was not the slightest sign of any descent. There is much encouragement to be offered by the procedure outlined by Aldridge for the cure of urinary stress incontinence. Although used by him for cystoceles that did not respond to other more simple types of repair, it has been of definite advantage to this patient. It is problematical what the present pregnancy will do to the plastic repair done one year previously.

References

1. Aldridge, Albert H.: *AM. J. OBST. & GYNEC.* 44: 398, 1942.
2. Price, P. B.: *Arch. Surg.* 26: 1043, 1933.

STRANGULATED HERNIA CONTAINING PREGNANT UTERUS AT TERM

CHARLES E. BOYS, M.D., F.A.C.S., KALAMAZOO, MICH.

THE importance of hernia as related to pregnancy is perhaps not sufficiently understood because of its infrequent occurrence. It does, however, occasionally become a real obstetric problem, and this is particularly true when most or all of the pregnant uterus has become strangulated in a hernial sac. In the earlier months, the pregnancy is often terminated by either spontaneous or therapeutic abortion. Even when the gestation continues to or near term, the termination may be spontaneous or by means of forceps through the natural passages, and a living child obtained. But when the uterus at or near term becomes strangulated, the seriousness of the condition is greatly increased.

Cases of strangulated hernia containing a pregnant uterus at or near term are rare. In an exhaustive search of medical literature only five case reports were found.

Manley¹ quotes Nocolaus Pol, 1531, an Italian physician who "removed a mature infant from a labial hernia." The mother died five days later but the infant survived. Bardeleben² demonstrated before a convention in Berlin, December, 1911, a case of pregnancy occurring soon after a pelvic laparotomy where the operative wound had broken down. This was followed by a hernia. At the time of the demonstration the gestation was in the eighth month and healed abdominal walls were "thin as paper." The author advised waiting until term; then, if difficulty presented itself in a spontaneous delivery, a section should be performed. No report later as to outcome. Typyakov³ reported the case of a woman, 23 years old, who was five months pregnant with the uterus strangulated in a subumbilical hernia. She developed severe abdominal pain which suggested that an abortion was likely, and an operation was advised. The hernial ring was incised, the uterus replaced in the abdomen and the hernia repaired. The patient recovered, went to term, and had a normal delivery. Cartaya⁴ reported a case in which a uterus the size of a four and one-half months' pregnancy became strangulated in an incisional hernia. Severe abdominal pain and vomiting ensued. Mechanical attempts at reduction failed and operation was advised. As in the case of Typyakov, the constricting ring was cut, the pregnant uterus returned to the abdominal cavity, and the hernia repaired. The patient went to term and had a normal delivery.

The most typical case was reported by Rosner.⁵ The patient was 30 years old and had had four pregnancies, the last one six years before. A subumbilical hernia had been present for two years before the present pregnancy. Abdominal pains developed at six months' gestation and operation was advised, but it was refused. Nothing more was heard of this patient until she was at term. She then developed severe pains which continued for forty-eight hours,

when it was determined that the pregnant uterus was entirely irreducible. Cesarean section was advised, but after opening the abdomen a Porro operation was decided upon and carried out. The mother recovered without complication but the infant died on the day of delivery from what was diagnosed clinically as congenital heart disease. An autopsy was not performed.

Because of the apparent rarity of this condition the following case is reported.

Case Report

Mrs. A. M., a white married woman, aged 37 years, was a para xi at term and had been in unusually severe labor for fourteen hours without measurable progress when first seen by the writer. She had had a supraumbilical hernia for several years which had been the cause of considerable trouble in three previous labors and especially with the last one, about eighteen months before the present delivery. Previous deliveries, however, ultimately were accomplished without interference, except the use of a tight abdominal binder during labor.



Fig. 1.—Strangulated hernia containing pregnant uterus at term. (Author's case.)

Examination showed the patient to be a woman of average size and nutrition. From the upper abdomen a tumor was observed apparently protruding through a median cleft in the abdominal wall above the umbilicus. Between pains the mass extended 17 cm. above the normal curve of the abdomen, and during pains it was about 7 cm. higher still. Ulcers each about 4 cm. in diameter were present in the overlying skin, due to irritation from adhesive straps which had been used unsuccessfully by the patient to control the hernia. Enormous varicosities were present in both lower extremities, but no palpable thromboses were found. Blood pressure was 140/90, pulse 88, temperature 97.8° F., and respirations 22. Urine was normal. Blood: red blood cells 3,540,000, white blood cells 10,900, hemoglobin 8.8 Gm., color index 0.78, and blood type 4. X-ray examination disclosed a full-term fetus with head not engaged. The uterine contractions recurred at from three- to five-minute intervals and were unusually violent, due partly to the strangulation. Rectal examination failed to reveal any fetal presenting part, nor any effacement or dilatation of the cervix, which was very high. Vaginal examination was not made, but no vaginal bleeding was evident. A diagnosis of strangulated abdominal (supraumbilical) hernia, with incarcerated pregnant uterus at term,

was made. Mechanical attempts to reduce the hernia were futile, and cesarean section was carried out at once.

After excising a considerable amount of skin to eliminate the infective cutaneous ulcers, the tumor was well exposed and found to consist of the entire fundus and about half of the corpus with enormously varicose broad ligaments. Reduction of the mass was impossible without enlarging the already large fascial ring with resulting increased difficulty of hernial repair. A classical section was performed because the lower uterine segment was unapproachable without enlarging the ring.

On incising the corpus, a large placenta was found immediately underneath. The buttocks and both lower extremities of the fetus were incarcerated immediately under the placenta. Of necessity the placenta was quickly removed first, followed by the fetus as a breech presentation. The amount of bleeding was not unusual, and the baby cried lustily almost at once. The infant, a girl, weighed 10 pounds and 14 ounces.

The uterine incision was sutured with four layers of No. 1 chromic catgut, and on account of its diminished size, the uterus became easily reducible. The surplus tissue of the hernial sac was excised, the peritoneum sutured, and the fascia closed by imbrication, using catgut sutures. Silkworm-gut was used for retention sutures and Nylon for the skin.

There was some breaking down of the superficial part of the wound by the tenth day and the hernioplasty was only partially successful; yet enough so, that eighteen months after the operation, the patient delivered a twelfth baby weighing 8½ pounds, following a three-hour labor, without incident.

A mild degree of thrombosis in the superficial veins developed a few days after operation in the left and then in the right popliteal regions. These were painful and tender and attended with a moderate degree of swelling of the lower extremities, but the condition had largely subsided when the patient left the hospital on the twenty-fourth postoperative day.

The baby had an entirely normal postdelivery course.

References

1. Manley, T. H.: Med. News 76: 130, 1900.
2. von Bardeleben: Ztschr. f. Geburtsh. u. Gynäk. 70: 709, 1912.
3. Typyakov, V. V.: Med. Obozr. 44: 409, 1895.
4. Cartaya, Francisco R.: Rev. méd. cubana 47: 343, 1936.
5. Rosner, Aleksander: Prezegl. lek. 43: 597, 1904.

GAS BACILLUS INFECTION OF THE UTERUS TREATED WITH PENICILLIN

GWEN S. HUDSON, M.D., AND M. PIERCE RUCKER, M.D., RICHMOND, VA.

THE gas bacillus is widely distributed in nature. It is a normal inhabitant of the intestinal tract of man and is found in the vagina of 4½ to 8 per cent of pregnant women.^{1, 6, 7} Falls² recovered the organism from the blood stream of a puerpera who had no symptoms of infection. Not only is the *Clostridium welchii* well-nigh everywhere but it is a spore-bearing organism that withstands boiling and is resistant to ordinary measures of sterilization. Rendle-Short³ believes that the pubic hairs become contaminated by feces, whence the germs are introduced into the vagina by the examining finger. In view of these facts it is difficult to explain why infection with this bacterium is not more common than it is. We have seen only three proved cases and one suspicious case in a combined experience of forty-five years. The latter was seen by the senior author a number of years ago. A Negro woman, who was admitted to St. Philip Hospital after an abortion, died in a few hours with symptoms strongly suggestive of gas bacillus infection. The uterus crepitated after death, but at autopsy only the colon bacillus was found.

Varying pathogenicity is one explanation that is advanced to explain the infrequency of genital tract infection. Usually the organism needs dead or devitalized tissue in which to get a start. Once it gets a start and builds up virulence, it produces a profound and usually a rapidly fatal illness. As would be expected, infection with the Welch bacillus is more frequent with abortions than with full-term deliveries. There is more trauma connected with induced abortions and usually the fetus dies before it is expelled. With term or near-term deliveries, placenta previa may be a predisposing factor. Two fatal cases of placenta previa treated with Willet's forceps have recently been reported in England.⁸

Criminal abortions furnish ideal conditions for this type of infection. In the first place the unscrupulous operator is not likely to be scrupulously clean. In the second place, he or she repeats the instrumentation until results are obtained, i.e., the death of the fetus. After the uterine cavity is infected and the fetus is killed, the patient is left to shift for herself. In all our cases, the patients entered the hospital with pubic hair intact. What other breaches of technique had been committed we had no way of knowing. However, not all gas bacillus infections occur in criminal abortions. Sandusk and Manahan⁵ report a case in which a therapeutic abortion for severe anemia was done at the Johns Hopkins Hospital.

Russell and Roach,⁴ who reported 17 cases, divided them clinically into three groups. When the infection is limited to the fetus and endometrium, with or without physometra, there are no characteristic symptoms. The diagnosis is made by either blood culture or uterine culture. They had six such cases with no maternal death. When the uterine wall is invaded, uterine pain with circulatory collapse is the outstanding symptom. There may or may not be crepitation upon manipulation of the uterus. They had four such cases with three maternal deaths. In one case, gas in the uterine cavity and in the uterine wall was demonstrated by x-ray. In the third group, the blood stream is invaded. There are a chill at onset, nausea and vomiting, jaundice, severe headache, and intense abdominal pain. The urine is often coffee-colored and there are cyanosis and shock. The fatal cases have gas in the lochia. Russell and Roach had seven such cases with six deaths.

The diagnosis depends upon demonstrating the organisms either in blood cultures or in cultures from the uterus. It should be suspected in any severe and rapidly progressive infection, especially if there is evidence of gas formation. This suspicion is heightened when an abortion has been induced outside of a hospital.

The course of the disease is frequently so rapid that no time should be lost in beginning treatment. The patient may die within sixteen hours from the time of the interference. All our cases support the thesis that treatment must be started early.

On Oct. 28, 1941, a 23-year-old unmarried Negro multipara was admitted to St. Philip Hospital with the history of having fallen on her right side the day before. Her last menstrual period began on July 15, 1941. There was no history of an attempted abortion. She looked sick and terrified. There was a trickle of blood-tinged watery fluid from the vagina. Her temperature was 103.4° F., pulse 122, respiration 44, blood pressure 100/60. The fundus was 23 cm. above the pubis and some crepitation was felt about the fundus. Hemoglobin was 76 per cent; red blood cells, 4,260,000; white blood cells, 8,600; polymorphonuclear leucocytes, 86 per cent. She was catheterized but no urine was obtained. Possible diagnosis included: premature separation of the placenta, ruptured uterus, infected abortion with pregnancy of six months. X-ray of chest showed nothing abnormal except the suggestion of free air under the right diaphragm. This suggested a ruptured viscus to one examiner. Six hours after admission to the hospital she suddenly became restless with rapid breathing, and died.

At autopsy the following afternoon, the body was bloated beyond recognition. Gas welled from all tissues and the viscera were all necrotic. The uterus was filled with gas and its inner surface was almost black in color and covered by a rough, shaggy exudate. No cervix was distinguishable. There were no uterine contents. Culture of intraperitoneal fluid showed *Cl. welchii*.

On Jan. 18, 1944, a 17-year-old unmarried white girl was admitted unconscious to the Johnston-Willis Hospital. Her temperature was 101° F. and she looked to be at term. A rectal examination was made and there was an explosive escape of gas from the vagina. In several hours she expelled a six-month macerated fetus and died before the placenta was delivered. Her stay in the hospital was less than twelve hours. Her treatment besides delivery care consisted of a blood transfusion.

It was evident that only a miracle drug could have saved these patients. Penicillin was not available at the time. Theoretically, it is the drug for the purpose because it is effective not only against *Cl. welchii* but also against many of the organisms that are so frequently associated with it in postabortal infections. In case of wound infections, penicillin has been found to be effective against gas bacilli in the blood stream but has no effect upon the bacilli growing in dead tissue. Débridement is as necessary when penicillin is used as it was formerly. By the same token, treatment of postabortal and postpartum infections with penicillin should be combined with local treatment.

Case Report

The patient, admitted to the Johnston-Willis Hospital, Nov. 25, 1944, was 29 years old, white, single, height 5 feet 7½ inches, weight 196 pounds. She said she had had nephritis at 8 years of age, but otherwise had been in good health until the present illness. Her menses had been regular until August 24 to 28. There had been no bleeding since until the day before admission. She had had some nausea and vomiting earlier, and had some headache and edema of her feet. For the past eleven days an unnamed woman had injected soapsuds for the purpose of producing abortion. She had had some abdominal cramping and pinkish vaginal discharge three days before admission. The day before admission bleeding became more profuse and she passed some clots.

Because of a high fever (103° F.) on November 25, she called for medical aid and was admitted ambulatory to the hospital.

On admission she did not appear ill except for having labor pains; temperature was 99.8° F., pulse 86, blood pressure 112/98. At 12:45 P.M., while in bed, she aborted a fetus 20 cm. long with its placenta intact. There was no excessive bleeding. She was given sulfathiazole, 7½ grains every four hours, although her temperature came down to normal the same day. Urinalysis was negative; hemoglobin, 85 per cent; white blood cells, 35,400; polymorphonuclear leucocytes, 92 per cent.

The following day, November 26, the sulfathiazole was discontinued because she had some vomiting and said a doctor had told her she could not take sulfa drugs. At 9:30 P.M. she was found to be in profound shock with cold clammy skin, pulse 110, thready; blood pressure unobtainable. There was no visible bleeding. She was given intravenous glucose in saline, 2 ampules of Cortate, and the foot of her bed was raised.

The next morning (November 27) her temperature was 98° F., pulse 88, blood pressure 92/?. The uterus was hard, tender, about the level of the umbilicus. She did not void that day. A little urine was obtained by catheter. It had a specific gravity of 1.030 and showed a trace of albumin. Red blood cells 5.49 million; hemoglobin 100 per cent; white blood cells, 41,450. A blood culture was taken for *Cl. welchii* which proved negative. She could take only small amounts of fluid by mouth and was fed glucose intravenously. Penicillin was begun; 20,000 units every three hours intramuscularly. She required morphine for pain which appeared to be increasing.

On the third day (November 28) the red blood count was 6.36 million; hemoglobin, 135 per cent; white blood cells, 40,000; polymorphonuclear leucocytes, 90 per cent. She still did not void, but began to void the next day. Her temperature rose to 99.4° F.; then in the succeeding days became subnormal, being as low as 96° F. on the fourth and fifth days post abortal. This was puzzling as she appeared very ill. Her pulse on the fourth day rose to 140, then subsided to 90. At times during this period, she would moan for hours with pain, her uterus being exquisitely tender, as were also the flanks to a lesser extent. The uterus was slightly higher in the abdomen. She still took only fluids by mouth. On the sixth day a flat x-ray of her abdomen failed to show gas in the uterus.

She gradually became more comfortable, and on the ninth day post abortal the penicillin was discontinued, although she still had some generalized abdominal pain. Her uterus was felt 2 fingerbreadths below the level of the umbilicus and was moderately tender. Three blood cultures had been negative, but a culture from the cervix indicated the presence of *Cl. welchii*.

On the tenth day (December 5) she became markedly worse; her temperature was 100° F. She had severe constant abdominal pain and the uterus appeared to be enlarging; red blood cells, 3.58 million; hemoglobin, 75 per cent; white blood cells, 14,950; polymorphonuclear leucocytes, 89 per cent. A fourth blood culture was taken which proved negative. She was restarted on penicillin, 20,000 units every three hours intramuscularly, and given sulfadiazine, 30 grains, for a first dose, then 15 grains every four hours by mouth. She was also given an intrauterine douche of zinc peroxide paste of which almost 5 ounces entered the uterus. The foot of the bed was elevated during this procedure and remained so for one-half hour.

During the next two days (December 6 and 7) she became more comfortable and her temperature was no higher than 99.4° F. Her uterus shrank to halfway between the umbilicus and pubis. On the twelfth day (December 7) the intrauterine douche was repeated but only 1 to 2 ounces would enter the uterus. On the thirteenth day (December 8) the penicillin was discontinued. On the fourteenth day (December 9) she had some nausea and vomiting. The sulfadiazine level had gone from 9.8 on the eleventh day to 13.3 on the fourteenth day. The dosage was then reduced.

On the seventeenth day post abortal (December 12) she developed symptoms typical of a gall-bladder attack with pain and tenderness under the right costal margin, associated with nausea and vomiting. Morphine was required to relieve the pain. On the eighteenth day (December 13) her temperature rose to 101.6° F. A catheterized urine specimen showed acid reaction and a trace of albumin, and 35 to 40 white blood cells per high-power field with clumps of pus cells; red blood cells, 3.16 million; hemoglobin, 68 per cent; white blood cells, 19,750; icteric index, 53. The medical consultant (Dr. T. D. Davis) considered the attack to be a hepatitis, possibly incident to sulfonamide therapy. Her uterus was scarcely palpable and not tender, and it was thought that her hepatitis had nothing to do with her initial infection. However, she was given penicillin, 20,000 units intramuscularly, from the eighteenth to the twenty-first day. She gradually improved and was discharged well on December 22, twenty-nine days post abortion.

Summary

A case of postabortal infection with *Clostridium welchii* is reported, in which treatment with penicillin apparently confined the infection to the uterus. However, it had no effect upon the process within that organ. The uterus continued to enlarge and was exquisitely tender until the patient was given, in addition, sulfadiazine, and local treatment with zinc peroxide. Recovery was then uneventful except for an attack of hepatitis on the seventeenth and eighteenth postabortal days. Our thanks are due to Dr. T. D. Davis for this valuable advice in outlining the treatment in this case.

References

1. Bysshe, S. M.: AM. J. OBST. & GYNEC. 35: 995, 1938.
2. Falls, F. H.: AM. J. OBST. & GYNEC. 25: 288, 1933.
3. Rendle-Short, Coralie: J. Obst. & Gynaec. Brit. Emp. 49: 581, 1942.
4. Russell, P. B., Jr., and Roach, M. J.: AM. J. OBST. & GYNEC. 38: 437, 1939.
5. Sadusk, J. F., Jr., and Manahan, C. P.: J. A. M. A. 113: 14, 1939.
6. Sadusk, J. F., Jr., and Manahan, C. P.: AM. J. OBST. & GYNEC. 41: 856, 1941.
7. Salm, R. J., Jr.: Obst. & Gynaec. Brit. Emp. 41: 121, 1944.
8. Browne, F. J.: J. A. M. A. 113: 1746, 1939.

OVARIAN PREGNANCY

J. B. BALLINA, M.D., AND N. E. CHIODI, M.D., BALTIMORE, MD.

(From the Gynecological Service of St. Joseph's Hospital)

BECAUSE of its comparative rarity, ovarian pregnancy is of great interest. The number of proved reported cases is still small, therefore reports of a single case may be recorded.

The case which we present is that of a 26-year-old white woman, admitted on Nov. 14, 1944, with the diagnosis of ruptured ectopic pregnancy. The patient had been well until that morning when she was suddenly seized with severe sharp pain in the region just to the left of the umbilicus. There was no nausea or vomiting associated with the pain. A vaginal discharge was present and described to be thick and tenacious. Menses had always been irregular as to time of occurrence and duration. Her last menstruation was on Oct. 5, 1944, at which time she bled for four days. The previous menses occurred on Sept. 15, 1944. The November period did not take place and there was no spotting or brownish discharge as far as the patient could ascertain.

Blood studies on admission showed a red blood count of 4,570,000, white blood cells 17,600, with 80 per cent hemoglobin. Urinalysis: specific gravity, 1.022; reaction, acid; sugar, negative; albumin, faint trace. Microscopic examination of urine, essentially negative. Blood chemistry: blood sugar, 118; nonprotein nitrogen, 31. Serology was negative.

Physical examination revealed a thin woman in acute distress. Blood pressure, 132/60; pulse rate, 100. Heart and lungs were essentially negative. Inspection of the abdomen revealed a slight elevation just to the left of the umbilicus. The patient's legs were drawn upward in an effort to relieve the pain. On palpation, there was marked tenderness about the umbilicus, and a mass about the size of a lemon could be felt in this area. Dullness was percussed in both flanks.



Fig. 1.—Section of white tissue found in blood clot, showing presence of fetal villi and Langhans's and syncytial cell masses.

Pelvic Examination.—The external genitalia were normal; no glands were palpated. The cervix was extremely soft and deviated to the left vaginal wall. The fundus of the uterus was pushed to the right. The right adnexa were normal. The left adnexa presented a small tumor in the region of the left ovary which confirmed the abdominal palpation. It

is interesting to note that during pelvic examination the patient experienced for the first time a burning pain in the left shoulder coupled with shortness of breath and pain on breathing.

Following examination, laparotomy was decided upon. A low midline incision was made under gas-oxygen-ether anesthesia. Upon opening the abdominal cavity, a considerable amount of free blood was found. This was immediately suctioned from the cavity. The pelvic organs as well as the abdominal organs were explored. The right tube and ovary were normal; the left ovary was enlarged with evidence of hemorrhage on its medial aspect. It was connected with the uterus by the ovarian ligament. The tube was entirely discrete from the ovary. The surface of the tube was smooth and not injected. Its fimbriated end was normal in every detail. Since the tube was normal, it was not removed. The meso-ovarium vessels were then doubly ligated and the ovary removed.

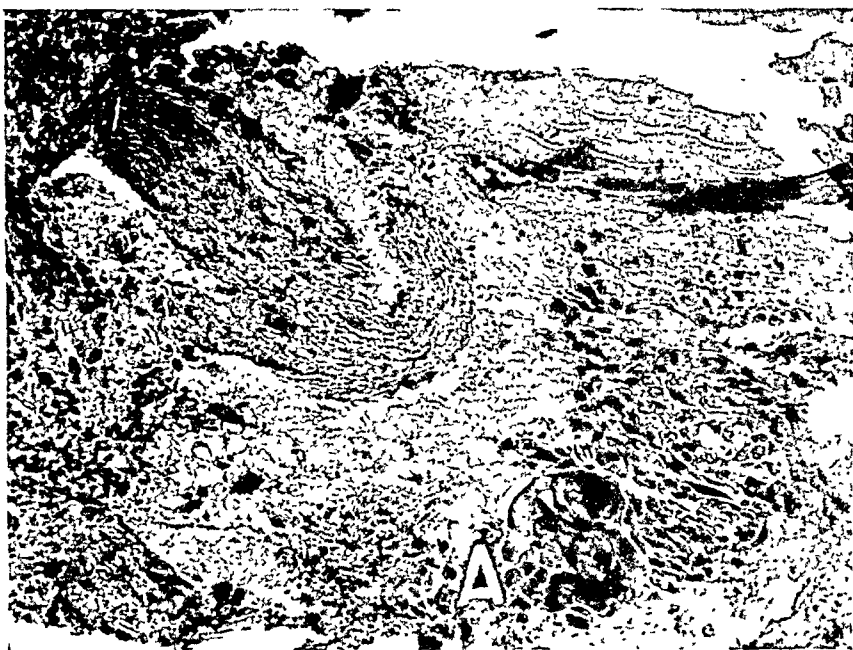


Fig. 2.—Section through ovary showing presence of syncytial and Langhans's cells (A) in contiguity with ovarian tissue.



Fig. 3.—Section showing presence of a group of Langhans's cells (B) adjacent to a portion of the corpus luteum (A).

Histologic Examination.—The gross specimen consisted of an ovary which measured 4 by 5 by 1 cm. It was covered with blood clots and contained at one point a red mass measuring 1 cm. in diameter. Scattered within the clots were fragments of white tissue. Microscopically, sections through the white mass revealed fragments of placental tissue (Fig. 1).

Examination of a section of the ovary showed a defect on the surface which was lined in part by an accumulation of large irregular cells containing large irregular nuclei. These cells resembled syncytial cells (Fig. 2). There was no distinct boundary between these masses of cells and the adjacent ovarian tissue. Another section of the ovary presented a large intact corpus luteum. Here again, there were seen within the adjacent tissue groups of cells which resembled Langhan's cells (Fig. 3). Some few resembled syncytial cells. Some hemorrhagic extravasation was present in the adjacent tissue.

Pathologic Diagnosis.—(1) Ruptured ovarian pregnancy; (2) corpus luteum of pregnancy.

Comment

The case just described seems to fulfill the criteria set up by Spiegelberg. There are some authorities on the subject of ovarian pregnancy who think that serial section of the salpinx must be examined microscopically to distinguish between a primary and secondary ovarian pregnancy. In our case the Fallopian tube was not removed. Since the tube was not edematous or injected and, most important of all, was in no way connected with the ovary, it was decided to leave the tube in situ. Because of this gross observation, together with the pathologic findings described above, we feel that this case is one of primary ovarian pregnancy.

Necrology

RAYMOND EDWARD WATKINS, M.D., a member of the Advisory Editorial Board, died Tuesday, Aug. 7, 1945, of a coronary seizure. Born in 1882, he graduated from the University of Illinois College of Medicine in 1909. Long prominent as a teacher and practitioner of the specialty in the Pacific Northwest, he headed the Department of Obstetrics and Gynecology of the University of Oregon Medical School for many years. Dr. Watkins was a member of the American Gynecological Society, the Pacific Coast Surgical Association, the Pacific Coast Society of Obstetrics and Gynecology, and the American College of Surgeons.

J. K. B. E. SEEGAR, M.D., well-known gynecologist and obstetrician of Baltimore, Maryland, died there Aug. 24, 1945, at the age of 70. He was a graduate of the University of Maryland, in practice since 1900, a member of the Medical and Surgical Faculty, the American College of Surgeons, and of the staffs of the Bon Secours and St. Agnes Hospitals.

Department of Reviews and Abstracts

Selected Abstracts

Abortion

Rebbeck, E. W.: Ultraviolet Irradiation of Autotransfused Blood in the Treatment of Postabortional Sepsis, *Am. J. Surg.* 55: 476, 1942.

Treatment by autotransfusion of irradiated blood consists in the withdrawal of a predetermined quantity of blood from the patient, subjecting it after citration to a selected band of wave lengths of ultraviolet rays, and immediately returning it to the patient. This procedure was used in 21 cases of postabortional sepsis, 17 preoperatively, and 4 postoperatively. The operation performed in every case was dilatation and curettage. Only two of the patients had received chemotherapy and in these the sulfonamide had not proved efficacious. Twelve case reports are presented, showing striking results. It is claimed that with the autotransfusion treatment the following reactions can be observed clinically:

1. Attenuation and destruction of bacteria.
2. Inactivation of toxins and viruses.
3. Increased absorption of oxygen by the blood.
4. Increase in general resistance to infection.

FRANK SPIELMAN.

Hertig, Arthur T., and Livingstone, Robert G.: Spontaneous, Threatened and Habitual Abortion: Their Pathogenesis and Treatment, *New England J. Medicine* 230: 797, 1944.

The authors stress the pathogenesis of spontaneous abortion, and summarize the recent literature with respect to the treatment of the theoretically preventable forms of this condition, namely, threatened and habitual abortion.

The study is based on the analysis of 1,000 spontaneous abortions. A threatened abortion as defined by Rutherford requires that the patient pass an amount of blood by vagina, excluding cervical and vaginal lesions, sufficient to make a stain 5 cm. in diameter on a vulvar pad before the case was classified as a threatened abortion. The proportion of habitual abortion in all spontaneous abortions probably lies somewhere between 3.16 and 9.8 per cent.

Two main factors were operating to produce a spontaneous abortion, namely, those traceable to defects or abnormalities of the ovum, and those due to maternal causes. In the former category were 617 abortions, or 61.7 per cent of the series, whereas the remaining 383, or 38.3 per cent, were in the latter category.

The data on habitual abortion are apparently as varied as those resulting in a chance or single spontaneous abortion. Treatment should begin prior to conception, because the genesis of many abortions is laid during the time before the first missed menstrual period. The same over-all treatment is indicated as is advocated for threatened abortion, because of the present lack of more specific therapeutic knowledge.

On the basis of a series of 1,000 cases examined embryologically and pathologically, approximately one-third of spontaneous abortions are theoretically capable of being salvaged at the time the patient is first seen by the physician.

Approximately 60 per cent of threatened abortions under adequate treatment may fail to abort.

Threatened abortion should be treated by some potent corpus luteum preparation, or, if estrogens are demonstrably low, by the administration of these substances. These hormones should be supplemented by vitamins E, C, and K, and thyroid, in conjunction with a program of so-called "nutritional adequacy."

Habitual abortion should be treated in the same manner as is recommended for threatened abortion, except that treatment should begin prior to, or coincident with, conception.

JAMES P. MARR.

Garcia, Pedro: Postabortal Peritonitis, *Bol. Soc. chilena de obst. y ginec.* 8: 135, 1943.

Reviewing the records of Public Assistance Post 3 of Santiago de Chile, the author found 9 cases of postabortal peritonitis in 1942 and 10 in the first half of 1943, suggesting that the number of cases for 1943 will be at least twice that for 1942. In 1942 six patients, or 66.66 per cent, and in 1943 two, or 20 per cent, died. The same personnel was responsible for the diagnosis and surgical technique during both years. Therefore, the better results must be due to improved details in the treatment, such as intra-abdominal application of sulfonamides, prompt use of the Miller-Abbott tube, transfusion of plasma and blood, and sulfonamides by mouth and parenterally.

The importance of early diagnosis of peritonitis and of early intervention, which should be minimal, must be kept in mind. Before closing the abdomen an adequate amount of sulfanilamide must be placed in the cavity, especially in the cul-de-sac of Douglas. This is one of the most important factors in successful treatment. In addition, uninterrupted and periodic new doses of the drug must be given orally or parenterally. The Miller-Abbott tube is used to combat paralytic ileus, and the author has found it the decisive element in the improvement of some patients. It should be introduced early and by experienced persons. Transfusions of plasma are better than those of blood to combat shock. If blood must be used, transfusions must be small and repeated. The patient must be given large amounts of water and salt.

J. P. GREENHILL.

Gynecology

Williams, R. H., Weinglass, A. R., and Kay, G. A.: Thiouracil Storage in the Thyroid as Affected by Thyrotropic Hormone and Potassium Iodide, *Am. J. M. Sc.* 207: 701, 1944.

Thiouracil has recently been used in the treatment of thyrotoxicosis. It leads to a fall in the basal oxygen consumption to normal levels with an associated clinical improvement, and a decrease in the protein-bound iodine content of the plasma. The effectiveness of this drug in inducing these changes is due to its inhibitory action on the production of the thyroid hormone.

In order to determine the quantity of thiouracil stored in the thyroid, five series of guinea pigs were given thiouracil either alone or in combination with thyrotropic hormone and potassium iodide, for varying periods of time. The thyrotropic hormone was administered in order to stimulate thyrotoxicosis, and the iodide in order to reproduce the treatment of the thyrotoxic patient first with iodide and then thiouracil. Thiouracil was found to be more concentrated in the thyroid of animals receiving no thyrotropic hormone than in those receiving the hormone. However, those animals receiving iodide in conjunction with thiouracil and thyrotropic hormone showed a greater concentration of the thiouracil in the thyroid than either of the other two groups. The authors conclude that thyrotropic hormone given with thiouracil is much more goitrogenic in guinea pigs than is thiouracil alone. The thyrotropic hormone tends to decrease the amount of thiouracil stored in the thyroid while potassium iodide greatly increases the quantity stored.

FRANK SPIELMAN.

Arana, Vicente Mugica: Considerations on the Pathogenesis and Diagnosis of Genital Tuberculosis, Toko-Ginecl. Practica 3: 43, 1944.

The author discusses tuberculosis localized in the tubes and the uterus.

The tubes may be infected by the circulatory and lymphatic routes and by contiguity. In recent and superficial infection, the tube is reddened, the fimbriae are infiltrated; but the most typical lesion is found in the serosa in the form of small tubercles. The chronic process assumes the form of hydrosalpinx or pyosalpinx, often bilateral and mobile because of lack of adhesions. The symptoms vary.

The uterus is one of the most frequent sites of tuberculosis of the genital apparatus, being involved in 50 per cent of the cases. The disease is secondary.

Lesions of the cervix are rare and may present the aspect of endocervicitis or of tuberculous ulcer of its vaginal portion. The posterior aspect of the cervix is more often involved than the anterior.

In general, uterine tuberculosis may occur at any age but it is more common during the period of genital activity. Symptoms vary: besides small hemorrhages and general symptoms secondary to salpingitis and peritonitis which nearly always coexist, there is sterility, 5 per cent of which is due to uterine tuberculosis.

To discover genital tuberculosis, except in case of external lesions, it is necessary to think of it, because symptoms which permit making the diagnosis are rarely encountered. Because early tuberculosis of the genitalia is secondary, careful questioning nearly always discloses the primary focus. In clear-cut cases of active primary lesion, the presence of exudate in the peritoneal cavity, bilateral pelvic masses with little pain and with exacerbations, evening temperature, relatively low leucocytosis and sedimentation rate which does not correspond to the process found should arouse suspicion of tuberculous etiology of the tubal process, especially when these symptoms occur in a virgin.

The best method to establish the diagnosis of uterine tuberculosis is from the material obtained by curettage, part being reserved for histologic examination and part for animal inoculation. Prognosis is serious as to function but benign as to life. The only active treatment is ultraviolet irradiation which gives satisfactory results. Hygiene and diet must receive consideration. Roentgen rays in small doses may be used in inoperable cases and in those rebellious to physiotherapeutic treatment.

J. P. GREENHILL.

Duran, Alfredo: Spontaneous Amputation of Ovarian Tumors, Bol. Soc. chilena de obst. y ginec. 8: 129, 1943.

The author describes three cases which occurred among 172 patients with benign tumor of the ovary hospitalized during the past eight years, an incidence of 1.7 per cent. The three cases included two cystic teratomas and one fibroma. An acute abdominal picture, which corresponded to torsion of the pedicle that caused the amputation, was present in two patients and during the course of a pregnancy eighteen months previously in the third. In all three, the amputated tumors had not undergone any changes because they had acquired important new vascular connections.

Ovarian tumors which undergo torsion are usually those of average size. Pregnancy favors torsion. From the clinical point of view it must be remembered that absence of adnexae on one side is not always congenital but may be due to torsion. Amputation sometimes occurs without symptoms. Once detached, the tumor may undergo resorption or remain in the abdominal cavity. Resorption is rare and occurs especially with cystic tumors. When the amputated tumor persists in the abdomen, it may be found on the large omentum or broad ligament, in the cul-de-sac of Douglas or the ileocecal region. If nutrition is insufficient in the new localization, regressive changes occur in the tumor (calcification, etc.). When the tumor becomes adherent to neighboring parts, new vessels are formed and it may persist indefinitely and even increase in volume. Ovarian dermoid cysts are those which are detached most easily. In rare cases the detached tumor has presented tuberculous infection or carcinomatous degeneration.

J. P. GREENHILL.

Gynecologic Operations

Schneider, Nicholas A.: A New Operation for Shortening the Round Ligaments, South. M. J. 37: 434, 1944.

The author reports a new method of shortening the round ligaments in the correction of uterine displacement. A longitudinal incision is made along the round ligament and parallel to it. Flaps of the peritoneum are dissected back, exposing the ligament itself. The ligament is cut transversely and the proximal end ligated and carried along the distal portion of the ligament and tied to it where it emerges from the inguinal canal. In like manner the cut end of the distal portion is advanced along the proximal portion of the ligament and attached near the cornua. The ligaments then may be sutured together in their mid-portion. The peritoneum is closed over the shortened ligament.

The author recommends this operation on the basis of: (1) ease of performance, (2) preservation of normal anatomy, (3) less likelihood of intestinal complications, and (4) compatibility with pregnancy. Drawings describing the technique are presented.

WILLIAM BICKERS.

Harrell, William B., and Estevez, Rafael: Indications for Pelvioscopy in the Female, South. M. J. 37: 415, 1944.

The pelviscope is a diagnostic instrument which may often be substituted for exploratory laparotomy. Congenital defects such as bicornate uterus, absence of the pelvic structures, and the determination of sex in the hermaphrodite are positive indications for its use. For obtaining a biopsy of pelvic tumors, differentiation of pelvic endometriosis from other pelvic pathology, and the determination of the presence or absence of metastases, the instrument is useful. Large ovarian cysts can be aspirated. The differentiation between appendicitis and pelvic inflammation is made possible. Extrauterine pregnancies may be differentiated from other nonoperative pelvic pathology. The authors have recently used a long, dull hook for retracting the viscera and thus gaining better exposure. Sterilization by cauterization of the uterine cornua through the pelviscope is possible. The operation is done through a small stab wound with a minimum of trauma and shock. Photographs of the instrument are presented.

WILLIAM BICKERS.

Falk, Henry C.: Cornual Resection for the Treatment of Salpingitis, West. J. Surg. 52: 309, 1944.

Primary gonorrheal infection of the tubes occurs by direct extension along the cervical canal and endometrium. Gonorrheal endometritis can be demonstrated but is rarely diagnosed because its symptomatology is overshadowed by the salpingitis. The chronic pus tube is the result of repeated infection from the lower genital tract. In postabortal infections the bacteria enter the endometrium at the placental site and invade the parametrium by way of the lymphatics. Differentiation is made between it and gonorrheal infection by the location of the resulting inflammatory masses. In both cases the acute infection is managed conservatively. In the chronic, recurring salpingitis due to gonorrheal infection, however, surgery is indicated. The object of the surgery is to relieve symptoms and not necessarily to remove all pathology. Since the infection is seen in young women, conservation of the genital organs is desirable. Therefore, the author reports a study on 1,000 women treated by resection of the cornual ends of the tubes to prevent recurrence of the ascending infection. Clinical cures were reported in 85 per cent.

WILLIAM BICKERS.

Emmert, Frederick V.: Vaginal Hysterectomy, Surg., Gynec. and Obst. 79: 277, 1944.

The author presents 600 cases of vaginal hysterectomy with a three-year follow-up on 502 private patients and a six-month follow-up on 98 ward cases. The

operations were done under combined local infiltration and block anesthesia. The technique of the operative procedure, which is a modification of Dickinson's operation, is well illustrated and the various stages described in detail. Briefly, it consists of a vaginal hysterectomy, advancement of the bladder above and beyond the joined stumps of the broad and round ligaments, and finally an anterior and posterior repair. The results are reported as satisfactory in 87.33 per cent of the cases. Recurrences were present in 12.66 per cent and are reported as follows:

	Cases	Per cent
Cystoceles	36	6.0
Rectoceles	28	4.6
Enteroceles	5	0.83
Incomplete vagina	5	0.83
Urethrocele	2	0.33

L. M. HELLMAN.

Borras, Pablo: Myomectomy as Conservative Surgery, *Semana méd.* 51: 1334, 1944.

The author uses temporary ligation of the uterine arteries and makes an antero-posterior lozenge-shaped incision embracing the tumor zone as in fundus resection. If necessary, this incision can be prolonged; it restores normal uterine form when the organ is reconstructed. The author excises a wedge of muscle, conserving the myoperitoneal and myoendometrial planes. Then he sutures the myomucous flaps, obliterates the dead space of the extirpated tissue with a few interrupted sutures, and approximates the myoperitoneal flaps, being careful to adjust them correctly.

J. P. GREENHILL.

Labor, Management, Complications

Phaneuf, L. E.: Ruptured Uterus Following the Spinelli Operation for Inversion of the Uterus, *Am. J. Surg.* 56: 379, 1942.

The patient was 30 years old and had had two forceps deliveries. Ten weeks following the termination of her second pregnancy it was discovered that she was suffering from an inversion of the uterus which the author repaired, performing a Spinelli operation. Recovery was without incident. She became gravid for the third time two years after the operation, and because of the danger of rupture of the uterus, the author planned delivery by cesarean section well before her expected date of confinement. However, three days before that date, the patient suddenly showed evidence of an acute abdominal accident, and at operation a rupture of the uterus was found for which, following removal of a living fetus, a Porro operation was done. Convalescence for both mother and baby was normal.

Pathologically, the rupture was found to have occurred along the line of previous incision in the uterus incident to the Spinelli operation. There was degeneration and rupture of the scar with digestion of collagen in this area.

FRANK SPIELMAN.

Tollefson, Donald G.: Methergine (Synthetic Lysergic Acid Derivative), a New Oxytocic, *West. J. Surg.* 52: 383, 1944.

Methergine is a synthetic ergonovine whose activity on the animal and human uterus has been demonstrated. Unlike ergotamine it does not have any inhibiting effect upon the adrenaline response of isolated rabbit uteri. No evidence of toxicity has been demonstrated. In 200 patients who had received nembutal and scopolamine in amnesic doses during labor, 1 c.c. of methergine was given intravenously as soon as separation of the placenta was in progress. Action of the oxytocic was rapid, averaging 48 seconds. Estimation of the blood loss in this series was thought to average 98 c.c. During the puerperium methergine has been given in doses of 3 tablets daily and the lochia was noticeably reduced.

The author's experience with the administration intravenously immediately after delivery of the shoulders has not been good. He recommends administration immediately after spontaneous separation of the placenta has begun.

WILLIAM BICKERS.

Cooke, B. G.: Sudden Death in Labor, *Brit. M. J.* 1: 457, 1944.

This article consists of a detailed case report with the necropsy findings. The principal finding and the alleged cause of death was a small aorta and evidence of status lymphaticus. The author believes such a condition may account for sudden death in some cases, especially where there is shock as from a rapid labor, as in this instance.

His search of the literature failed to reveal a similar case.

FRED L. ADAIR.

Danforth, W. C.: Test of Labor, *Illinois M. J.* 86: 90, 1944.

The author makes a distinction between a "trial labor" and a "test labor." Both are indicated only in borderline contractions of the pelvic inlet. The importance of the use of x-ray pelvimetry is stressed and the necessity of having this done by those who are experienced in this method is emphasized. The purpose of the trial or test should be solely to determine whether or not the fetal head will enter the pelvic inlet. It, of course, has no place in contractures of the pelvic outlet. In summary, the author states "test labor must not be regarded as a substitute for careful prenatal study of any possible disproportion. There is never an excuse for clinical laziness, and most cases in which disproportion of any extent exists may be detected before labor begins. This makes it possible to use the abdominal delivery at the time of greatest safety, that is, as an elective operation. If a trial is to be had, the birth canal must be preserved from all contamination, and, in particular, no attempt at delivery from below should be made."

FRED L. ADAIR.

Roberts, Paul C.: The Use of Methergine (Synthetic Ergonovine) in the Third Stage of Labor, *West. J. Surg.* 52: 380, 1944.

Methergine, a new synthetic ergonovine, was administered subcutaneously to 26 cases and intravenously to 34 cases immediately after delivery of the baby. The dose was 1 c.c., which contained $\frac{2}{10}$ mg. of the drug. Careful attention was given to blood loss, reaction time, and duration of the third stage of labor. To measure the volume of blood loss, an oil silk drape was clipped above the episiotomy incision and carried to a clean receptacle, thereby forming a trough for the collection of uterine blood. The average blood loss in the methergine series was 181 c.c. and in the control series 247 c.c. The author has previously reported no reduction in blood loss following ergonovine administration. However, this can be explained by the improved technique now used for the management of the third stage. This includes immediate expression of the placenta when the first contraction is felt following intravenous medication and prompt uterine massage.

Duration of the third stage was shorter in the methergine series than in those patients receiving ergonovine. In 82 per cent the third stage was five minutes or less. The author advises manual removal of the placenta in those cases which have not delivered the placenta within twenty minutes. The reaction time following intravenous administration was thirty seconds. It differed from the ergonovine reaction in that the first contraction was very hard, and this contracted state persisted for several hours. It is emphasized that the incidence of retained placenta can be greatly reduced if expression of the placenta is accomplished within a few minutes after injection.

WILLIAM BICKERS.

McIntyre, W. Keverall: Injection of the Umbilical Vein to Prevent Postpartum Hemorrhage, *M. J. Australia* 2: 113, 1944.

The author has used this procedure in about 150 cases, and is convinced of its value, not only as a method of separation and delivery of a retained placenta, but more particularly as a method of preventing or minimizing postpartum hemorrhage. The author uses this method after any intrauterine manipulation. The procedure diminishes blood loss and shock, shortens the third stage, and flushes out the uterus and vagina. The solution must be injected rapidly, and the the solution must be of

such temperature that it reaches the uterus at about 115° to 120° F. At least a pint of hot normal saline solution should be injected, as the response usually begins when this amount has been reached.

WILLIAM BERMAN.

The Newborn

Macklin, Madge Thurlow: Erythroblastosis Fetalis: A Proposed Definition and Clarification of the Term, Am. J. Dis. Child. 67: 445, 1944.

The author defines erythroblastosis as a condition in which the blood of the fetus exhibits immature cells of the erythrocytic series which are not normal either as to type or as to quantity for the stage of development of the fetus.

This condition may be elicited by numerous factors, may or may not be accompanied with hemolysis, and may or may not be accompanied with extramedullary hemopoiesis. It includes hemolytic disease of the newborn as well as erythroblastosis due to factors other than hemolysis. When it is due to antigen-antibody reaction there will be hemolysis, with accumulation of iron in the fetal liver, and there will usually be persistent extramedullary hemopoiesis. This form of erythroblastosis is hemolytic disease of the newborn. In the majority of instances the hemolysis appears to be due to the Rh factor complex.

Factors such as anoxemia cause erythroblastosis as here defined, but not hemolysis.

A tentative explanation of the failure to find antibodies in the blood of the mothers of some fetuses showing erythroblastosis is advanced, based upon a supposed immaturity of the antigen as it exists in the immature red cell, with a corresponding specificity of the antibody for this particular antigen.

Another possible explanation is based on the recently discovered fact that there are at least six different Rh factors. Preparations of only the two commoner types of antigen are employed in the usual tests.

JAMES P. MARR.

Sievers, Jerome J., Knott, Leslie W., and Soloway, Herman M.: Penicillin in the Treatment of Ophthalmia Neonatorum, J. A. M. A. 125: 690, 1944.

The authors report the treatment with penicillin of eight cases of ophthalmia neonatorum. They started with 10,000 units of penicillin every three hours for a total of six doses. At first this was found to be inadequate, and was later changed so that the dosage was adjusted individually for each case. All except two of the cases responded to therapy within twenty-four hours, as manifested by subsidence of active inflammation. In the six cases that responded to the specific therapy, clinical recovery occurred in from three to six days with complete absence of purulent discharge, chemosis, and injection. The disappearance of specific organisms in smears and cultures was noted in from nine to twenty-four hours after beginning treatment with penicillin. One case developed an urticarial rash after the third injection of penicillin. The criteria of cure were (1) absence of clinical activity, (2) three negative smears of gram-negative intracellular diplococci, and (3) three negative cultures for gonococci.

WILLIAM BERMAN.

Item

American Board of Obstetrics and Gynecology, Inc.

Examinations

The next written examination and review of case histories (Part I) for all candidates will be held in various cities of the United States and Canada on Saturday, Feb. 2, 1946, at 2:00 P.M. Candidates who successfully complete the Part I examination proceed automatically to the Part II examination held later in the year. All applications must be in the office of the Secretary by Nov. 1, 1945.

All candidates are now required to be out of medical school eight years, and in that time they must have completed an approved one-year internship and at least three years of approved special formal training, or its equivalent by the preceptorship method under a recognized obstetrician-gynecologist or a diplomate of this Board, in the seven years following the intern year. This Board's requirements for internships and special training are similar to those of the American Medical Association, since the Board and the American Medical Association are at present cooperating in a survey of acceptable institutions.

A number of changes in Board regulations and requirements were put into effect at the Board's last annual meeting held in June, 1945. These were designed to aid civilians as well as candidates in the Service and have been incorporated in the *Bulletin of the Board*, copy of which may be obtained from the Secretary's Office, 1015 Highland Building, Pittsburgh 6, Pennsylvania.

All candidates are required to take the Part I examination which consists of a written examination and the submission of twenty-five case history abstracts, and the Part II examination which consists of an oral-clinical and pathology examination. The Part I examination will be arranged so that the candidate may take it at or near his place of residence, while the Part II examination will be held late in May, 1946, or early June, 1946, in that city nearest to the largest group of candidates. Time and place of this latter will be announced later.

For further information and application blanks, address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh 6, Pennsylvania.

PAUL TITUS, M.D.

Announcement

Twenty-Fifth Anniversary Issue

The editors and publishers of the JOURNAL are preparing a special number to commemorate the completion of a quarter of a century of uninterrupted publication. This will appear in December.

Correspondence

Venous Ligation in Obstetrics

To the Editor:

The present wave of enthusiasm for prophylactic venous ligation promises to reach alarming proportions, especially in certain quarters. The time has come to introduce a note of caution regarding its obstetric application.

Recently, the writer witnessed bilateral femoral vein ligation in an apparently normal 24-year-old primipara four days post partum. At the time of operation, no clot could be aspirated from the right side. The left vein was tied without effort to establish presence or absence of thrombus. Immediately post partum, the patient, who was delivered by a member of the visiting staff, complained of difficulty turning in bed and of pain in the right leg. She was more comfortable in the erect position, and daily the ability to move improved and the leg pain diminished. There was definite pain over both sacroiliac joints posteriorly, and over the symphysis pubis. On the evening of the third day, an isolated "spike" to 101.0° F. occurred in the temperature curve. This fever lasted less than eight hours, and when the decision to ligate veins was made, the temperature was 99.0° F. and the pulse rate 80 beats a minute. So far as the writer can ascertain, the motivating factor in the decision to operate was pain in the calf of the right leg on dorsiflexion of the foot (Homan's sign). The day following operation, the temperature was 101.2° F. but returned to normal on the second postoperative day. On the third postoperative, and the seventh postpartum day, a febrile reaction began, lasted six days, and three times the temperature curve reached a peak of 102.0° F. The patient complained of numbness in both legs and there was tenderness, swelling, and redness, especially on the right. At least twice during the course of this febrile illness the patient experienced definite chills. Saphenous vein ligation was refused by the patient, who was discharged in a wheel chair on the fourteenth postpartum day. Both legs were considerably swollen six weeks post partum.

"Phlebothrombosis" or "bland" thrombosis tends to occur in patients over 40 years of age, especially after prolonged bed rest. In addition to pain in the calf of the leg, an ascending "step ladder" pulse and Homan's sign represent the principal diagnostic points. Phlebography, once popular, is employed less and less as a diagnostic measure. All writers set considerable store by Homan's sign. Allen states unequivocally that a positive Homan's sign is "pathognomonic when present" and that "if discomfort in the calf muscles or the popliteal space is experienced during this maneuver, *one can be sure* [italics mine] that deep venous thrombosis exists." Having elicited a positive Homan's sign some months ago in a pregnant woman who spent the previous day refinishing the floor of her apartment, I am inclined to believe that sore muscles may occur without necessitating a diagnosis of "bland" thrombosis.

Since all writers emphasize that "bland" thrombosis shows a definite predilection for the upper age groups (Allen's series of 202 patients showed 81 per cent over 40 years of age), and since I could not remember a single death from embolus as a sole cause in the University of Iowa series, it was decided to collect some information concerning the incidence of fatality from embolus in obstetric practice. Letters were written to the chiefs of representative clinics in various parts of the United States. Their replies were generous and prompt, and data supplied are listed in the accompanying table.

From these figures, it is apparent that the chance any pregnant woman will die from embolus is 1 in 7,101. If we consider only obstetric patients whose puerperal courses were relatively normal, and exclude histories where there were complicating factors contributory to, or productive of, death, we find only four fatalities from embolus among 139,546 patients, or 1 in 34,886! In other words, the uncomplicated obstetric patient stands only one chance in almost 35,000 of embolic death from bland thrombosis. Stated differently, phlebothrombosis is virtually nonexistent among relatively normal puerperal women.

In the light of such figures, it is difficult to believe that prophylactic venous ligation will save the lives of many obstetric patients. In fact, the patient will experience far greater

INSTITUTION	PATIENTS (NUMBER)	FATAL EMBOLUS	
		TOTAL NUMBER	NONMORBID PUER- PERIUM NO ANTECEDENT COMPLICATION
St. Louis University Hospitals (Vogt)	15,095	3	*
Los Angeles County Hospital (Hanley)	46,395	6	*
St. Vincent's Hospital (L. A.) (Hanley)	12,000	0	
Chicago Lying-in (Dieckmann)	45,000	6	3
Margaret Hague (Cosgrove)	78,546	13	1
University of Iowa (Plass)	16,000	2	0
Totals	213,036	30	4

*Figures not available.

danger from the anesthetic and the operation than she will ever incur from phlebothrombosis. The obstetric patient, by and large, is a young woman. There is a growing tendency to get her out of bed early in the puerperium. The two chief causes of bland thrombosis, or phlebothrombosis, age and inactivity, are not commonly present in the obstetric patient.

There is no doubt that prophylactic venous ligation has a place in surgery and in geriatrics. I do not believe it has a place in routine obstetric practice. Enthusiasm for the new should not cause us to jettison the accumulated wisdom of the past.

(Signed) WILLIAM F. MENGERT, M.D.

2211 OAK LAWN AVENUE
DALLAS 4, TEXAS

ROSTER OF AMERICAN OBSTETRICAL AND GYNECOLOGICAL SOCIETIES*

(Appears in January, April, July, October)

- American Gynecological Society.** (1876) *President*, Edward A. Schumann, Philadelphia, Pa. *Secretary*, Howard C. Taylor, Jr. 842 Park Ave., New York, N. Y. Annual meeting cancelled.
- American Association of Obstetricians, Gynecologists and Abdominal Surgeons.** (1888) *President*, Lewis F. Smead, Toledo, Ohio. *Secretary*, James R. Bloss, 418-11th Street, Huntington, W. Va. Annual meeting Hot Springs, Va., Sept. 1944.
- Central Association of Obstetricians and Gynecologists.** (1929) *President*, John H. Moore, Grand Forks, N. D. *Secretary-Treasurer*, W. F. Mengert, Dallas, Tex. Annual meeting not announced.
- South Atlantic Association of Obstetricians and Gynecologists.** (1938) *President* Oren Moore, Charlotte, N. C. *Secretary*, T. J. Williams, University, Va. Annual meeting cancelled.
- A. M. A. Section on Obstetrics and Gynecology.** *Chairman*, Philip F. Williams, Philadelphia, Pa. *Secretary*, William Mengert, 2211 Oak Lawn Ave., Dallas Tex. Meeting cancelled.
- New York Obstetrical Society.** (1863) *President*, R. A. Hurd. *Secretary*, R. G. Douglas, 530 East 70th St., New York City. Second Tuesday, from October to May, Yale Club.
- Obstetrical Society of Philadelphia.** (1868) *President*, Charles A. Behney *Secretary*, John B. Montgomery, Pro tem, 1930 Chestnut St., Philadelphia, Pa. First Thursday, from October to May.
- Chicago Gynecological Society.** (1878) *President*, James E. Fitzgerald. *Secretary*, Herbert E. Schmitz, 25 East Washington Ave., Chicago, Ill. Third Friday, from October to June, Hotel Knickerbocker.
- Brooklyn Gynecological Society.** (1890) *President* Chas W. Mueller. *Secretary*, William T. Daily, 142 Joralemon St., Brooklyn, N. Y. First Friday, from October to May, Kings County Medical Society, 1313 Bedford Ave., Brooklyn, N. Y.
- Baltimore Obstetrical and Gynecological Society.** (1929) *President*, Lawrence Wharton. *Secretary-Treasurer*, John W. Haws, 9 E. Chase St., Baltimore, Md. Meets quarterly at Maryland Chirurgical Faculty Bldg.
- Cincinnati Obstetrical Society.** *President*, Edward Friedman. *Secretary*, Carroll J. Fair, Cincinnati, Ohio. Third Thursday of each month.
- Louisville Obstetrical and Gynecological Society.** *President*, Layman A. Gray. *Secretary*, E. P. Solomon, Hegburn Bldg., Louisville, Ky. Fourth Monday, from September to May, Brown Hotel.
- Portland Society of Obstetrics and Gynecology.** *President*, Charles Hunt. *Secretary-Treasurer*, Karl H. Martzloff, 808 Medical Dental Bldg., Portland, Ore. Last Wednesday of each month.
- Pittsburgh Obstetrical and Gynecological Society.** (1934) *President*, James S. Taylor. *Secretary*, Joseph A. Hepp, 121 University Place, Pittsburgh, Pa. First Monday of October, December, February, April, and June.
- Obstetrical Society of Boston.** (1861) *President*, George Van S. Smith. *Secretary*, Paul A. Younge, 101 Bay State Road, Boston, Mass. Third Tuesday, October to April, Harvard Club.
- New England Obstetrical and Gynecological Society.** (1929) *President*, Roy J. Hefferman, Brookline, Mass. *Secretary*, Fred J. Lynch, 475 Commonwealth Ave., Boston, Mass. Meetings held in May and December.
- Pacific Coast Obstetrical and Gynecological Society.** (1931) *President*, Goodrich C. Schaffer. *Secretary-Treasurer*, William Benbow Thompson, 6253 Hollywood Blvd., Los Angeles, Calif.
- Washington Gynecological Society.** (1933) *President*, James R. Costello. *Secretary*, Geo. J. Ellis, 1150 Connecticut Ave., N.W., Washington, D. C., Fourth Saturday, October to May.

*Changes, omissions, and corrections should be addressed to the Editor of the JOURNAL. The number after the name is the year of founding.

- New Orleans Obstetrical and Gynecological Society.** (1924) *President*, E. L. Zander. *Secretary*, R. A. Grasser, 2700 Napoleon Ave., New Orleans, La. Meetings held every other month.
- St. Louis Gynecological Society.** (1924) *President*, S. A. Weintraub. *Secretary*, Joseph A. Hardy, Jr., 4952 Maryland Ave., St. Louis, Mo. Meetings second Thursday, October, December, February, and April.
- San Francisco Gynecological Society.** (1929) *President*, Albert M. Vollmer. *Secretary*, Daniel G. Morton, University of California Hospital, San Francisco, Calif. Regular meetings held second Friday in month from October to April, University Club, San Francisco, or Claremont Country Club, Oakland, Calif.
- Texas Association of Obstetricians and Gynecologists.** (1930) *President*, T. F. Bunkley. *Secretary*, J. McIver, 714 Medical Arts Bldg., Dallas, Tex.
- Michigan Society of Obstetricians and Gynecologists.** (1924) (Formerly the Detroit Obstetrical and Gynecological Society.) *President*, Robert B. Kennedy. *Secretary*, Milo R. White, 2799 W. Grand Blvd., Detroit, Mich. Meetings first Tuesday of each month from October to May (inclusive).
- Obstetric Society of Syracuse Hospitals.** (1938) *President*, Edward C. Hughes. *Secretary*, Nathan N. Cohen, 713 E. Genesee St., Syracuse, N. Y. Meets second Tuesday of September, November, January, March, and May. Suspended for the duration.
- Alabama Association of Obstetricians and Gynecologists.** *President*, J. M. Weldon, Mobile, Ala. *Secretary*, Eva F. Dodge, Montgomery, Ala.
- San Antonio Obstetric Society.** *President*, I. T. Cutter. *Secretary*, S. Foster Moore, Jr., San Antonio, Tex. Meetings held first Tuesday of each month at Gunter Hotel.
- Seattle Gynecological Society.** (1941) *President*, Gerhard Ahnquist. *Secretary*, Roger E. Stewart, Stimson Bldg., Seattle, Wash. Meetings held on third Wednesday of each month.
- Denver Obstetrical and Gynecological Society.** (1942) *Secretary*, Emmett A. Mechler, 1612 Tremont St., Denver, Colo. Suspended during war.
- Wisconsin Society of Obstetrics and Gynecology.** (1940) *President*, Roland S. Cron. *Secretary*, Robert E. McDonald, 425 E. Wisconsin Ave., Milwaukee, Wis. Meetings held in May and October.
- San Diego Gynecological Society.** (1937) *President*, Geo. D. Huff. *Secretary*, D. Dalton Deeds, 2001 Fourth Ave., San Diego, Calif. Meetings held on the last Wednesday of each month.
- North Dakota Society of Obstetrics and Gynecology.** (1938) *President*, Ralph E. Leigh, Grand Forks. *Secretary*, G. Wilson Hunter, 807 Broadway, Fargo, N. D.
- Virginia Obstetrical and Gynecological Society.** (1936) *President*, A. L. Carson, Jr. *Secretary*, L. L. Schamburger, 628 State Office Bldg., Richmond, Va. Next meeting not announced.
- Columbus Obstetrical and Gynecological Society.** (1944) *President*, Sylvester Goodman. *Secretary*, Zeph J. R. Hollenbeck, 9 Buttles Ave., Columbus, Ohio. Meetings held last Wednesday of each month.
- Nassau Obstetrical Society.** (1944) *President*, Arthur C. Martin. *Secretary*, William S. C. Dolan, 2870 Northern Blvd., Manhasset, N. Y. Meetings, bi-monthly from October to May.
- Bronx Gynecological and Obstetrical Society.** (1924) *President*, Jacob Clahr. *Secretary-Treasurer*, J. Irving Kushner, 1840 Grand Concourse, New York, N. Y. Meetings, fourth Monday monthly from October to May.
- Washington State Obstetrical Society.** (1936) *President*, John H. Fiorino Everett. *Secretary*, H. H. Skinner, Yakima. Meetings, first Saturday of April and October.
- Kansas City Obstetrical and Gynecological Society.** (1922) *President*, J. Milton Singleton. *Secretary*, Richard C. Helman. Meetings, third Thursdays, September, November, January, March, and May, University Club.
- Los Angeles Obstetrical and Gynecological Society.** (1914) *President*, George E. Judd. *Secretary*, Carl E. Krugmeier, 2200 West Third Street, Los Angeles, Calif.
- North Carolina Obstetrical and Gynecological Society.** (1932) *President*, Frank Locke, Winston-Salem. *Secretary*, Wallace B. Bradford, Charlotte, N. C. Meetings semiannually.

American Journal of Obstetrics and Gynecology

VOL. 50

NOVEMBER, 1945

No. 5

Original Communications

PLACENTAL SENESENCE AND THE ONSET OF LABOR*

HOWARD STEPHEN MANDEL, M.D., SAMUEL GRAFF, PH.D., AND
ADA M. GRAFF, A.B., NEW YORK, N. Y.

*(From the Department of Obstetrics and Gynecology, and the Department of Biochemistry,
College of Physicians and Surgeons, Columbia University; and
The Sloane Hospital for Women)*

THE forces which initiate labor are completely unknown. Speculation couples the onset of labor with numerous factors, hormonal and otherwise, among them senescence of the placenta. The nine-month life span of the placenta may be merely coexistent with the period of gestation, or conceivably, may be inextricably interwoven with the timing and causation of the onset of labor.

On histological evidence, Grosser, Young, Bartholomew and Colvin, Eden, Fraser, Williams, Tenney and Parker, and others have concluded that the placenta is a senile organ at term. Yet, according to Smith and Smith, Cohen, Marrian and Watson, Probstner, and others, the amounts of estrogen and progesterone, presumably produced by the placenta, reach their highest levels at term. Is this apparent increase in functional activity consistent with the histological picture of increased fibrosis of the villi, fibrin deposition, infarct formation, endarteritis, and loss of the Langhans' cell layer?

By the use of chemical methods, previous workers have found it possible to correlate the morphologic picture and physiologic activity of any living tissue with its chronological age (See Cowdry). Robertson, studying the general problems of growth and age, observed that the nucleocytoplasmic ratio altered with the age and rate of growth of various tissues. Furthermore, this ratio consistently diminished with age, but most rapidly in the earliest stages of growth. Heulin confirmed this in plants, Le Breton and Schaeffer in chick embryos, Graff in guinea pig embryos. Thus, according to Le Breton and Schaeffer:

*This paper is part of a dissertation submitted by H. S. Mandel, M.D., in partial fulfillment of the requirements for the degree of Doctor of Medical Science.

DAYS OF DEVELOPMENT OF
CHICK EMBRYO8
10
13
16
20CHEMICAL NUCLEOPLASMATIC
RATIO10.7
8.8
6.65
4.9
3.5

Similar curves were derived by all authors. It was found also by both Robertson and Graff that specific tissues at stated ages have characteristic NCR's. Histologically, the NCR is defined as the ratio of volume of nucleus to the volume of cytoplasm; it may be approximated by measurement of relative cross-section area (Conklin). Chemically, we may define the NCR, perhaps with greater precision, as the ratio of active nuclear mass, chromatin mass, to total cytoplasmic mass. In practice, the cytoplasmic mass is measured by its protein nitrogen content; nuclear mass by its purine content, because purine is a definite stoichiometric constituent of the chromatin. Expressed mathematically*:

$$\text{NCR} = \frac{\text{Purine Nitrogen}}{\text{Total Nitrogen} - \text{Purine Nitrogen}}$$

Since the NCR decreases from youth, the period of greatest nuclear and cytoplasmic activity and growth, to old age, it is possible to determine the "functional" age of a tissue by measuring its NCR. Speculating on the general problem of the onset of labor, Danforth and Ivy suggested that a relation might exist between the age and the NCR of the placenta, and that the NCR might have some bearing on the onset of labor.

This paper reports first on our investigation of the hypothetical correlation between the chronological age of the placenta and its NCR during its life expectancy of nine months; second, on our inquiry into the possible relation between the "functional" age of the placenta as expressed by its NCR, and the onset of labor; and third, on our efforts to determine what if any related factors accelerate or retard both the aging process and the onset of labor.

The material studied consisted of human placentas collected from the delivery and operating rooms of the Sloane Hospital for Women. A series of placentas were obtained from normal patients with varying lengths of labor; toxemic patients† and those with missed abortions or stillbirths; patients who did not undergo labor but were subjected to cesarean section, hysterotomy, or therapeutic abortion; and patients who were three or more weeks overdue. To date, over 185 placentas have been collected.

TABLE I

<i>Under 3 Months</i>	28	
3-6	9	
6-9	32	(A, no labor—40
<i>All term</i>	68	(B, some labor, cesarean—6
<i>Overdue</i>	2	(C, ordinary labor—8
<i>Mild toxemia</i>	23	
<i>Severe toxemia</i>	12	
<i>Missed abortions and stillbirths</i>	14	

186

*It is obvious that the NCR so defined and hereinafter applied in this article is not strictly comparable to the histological NCR. There is considerable evidence, however, to the effect that the two are related by a simple factor in any given system.

†Mild toxemias are here defined as those cases in which there were two or more blood pressure elevations of 120/90 or over during pregnancy, with or without albuminuria, excessive weight gain, or edema, but with symptomatology of insufficient severity to warrant hospitalization. The severe toxemias were classified as pre-eclamptic and were almost invariably hospitalized prior to the onset of labor. No eclamptics were included in this study.

The NCR was measured chemically by the method of Graff and Maculla. This method involves hydrolysis of a representative sample of tissue and the subsequent estimation of total nitrogen in one aliquot, and purine nitrogen in another suitable aliquot portion of the hydrolysate. Analyses were carried out in duplicate whenever possible, and values discrepant by more than 2 per cent were discarded. Therefore, all values herein reported have an analytical error of less than 5 per cent. The preliminary preparation of a representative sample occasioned some difficulty and considerable uncertainty. As is well known, there is a sharp increase in the activity of nucleoclastic enzymes immediately following the death of any tissue. The possible loss of purines, reflected as decreased NCR, was minimized by prompt preparation of the specimen immediately after delivery, and early refrigeration. Since it is possible to prepare high molecular weight fibrous desoxyribonucleoprotein as late as one hour after delivery, we feel that any errors from this cause are of negligible though incalculable magnitude. However, we exhibit evidence later herein that autolytic losses can be very large indeed when death *in situ* precedes handling by many hours, weeks, or even months, as, for example, in missed abortions.

Errors of considerable magnitude are also introduced by virtue of the fact that the placenta is a highly vascular organ, and retains large volumes of blood after delivery. The amounts of blood retained vary greatly depending upon the age of the placenta, length of labor, and methods of delivery. Heat coagulation and filtration were found to be cumbersome and the results inconsistent because of retained blood. Search for a correction factor (e.g., iron determinations) was fruitless, and washing was perforce necessary.

The placenta was placed in approximately isotonic saline-citrate solution immediately after delivery, and dissected so as to remove membranes and obvious blood clots. It was then divided in a meat chopper and washed with additional portions of the saline-citrate solution until the waters coming through a gauze or metal strainer were but faintly colored. The washing was carried out as speedily as possible to minimize possible solution and decomposition, no attempt being made at thorough washing but rather to accomplish a consistent and reproducible degree of washing. A number of analyses were carried out for the purpose of determining the efficiency of this washing method. Eight full-term placentas were so treated and the mean NCR of the eight analyses was 3.27. Four full-term intact placentas were perfused immediately after delivery with citrate-saline solution and yielded NCR values of 3.23, 3.29, 3.67, and 3.47, respectively, without further treatment. The mean NCR was 3.41. Perfusion was necessary to establish the fact that washing did not affect the NCR materially. When a portion of placenta which gave 3.47 per cent after perfusion was divided in the meat chopper, again washed in citrate-saline and drained three times, a value of 3.45 was found. Upon additional washing and standing in cold saline-citrate for one hour, another portion of the placenta yielded the identical value. The empirical method of washing as given above was adopted then on the basis of the foregoing evidence. It was, of course, especially convenient since it permitted similar handling of all placentas. Ruptured organs and early placentas impossible to perfuse could be as easily treated as the older, intact ones.

The estimation of the chronological age of the placenta is uncertain and unreliable. A minimum of two and a maximum of four weeks' error may be automatically assumed to be inherent in our present methods of estimation of the beginning and end of pregnancy. Likewise, the completeness of the dissec-

tion introduces a factor of quantitative importance. The membranes of any placenta are tissues of relatively inactive and sparsely nucleated character. In the younger placentas especially, in which the membranes occupy a relatively larger proportion, lack of complete dissection will lower the NCR. Thus, in a nine weeks' placenta the NCR for membranes and some decidua was 2.66, for chorionic villi 6.20.

For the afore-mentioned reasons, therefore, we have attempted to increase the size of each series of placentas so as to produce distribution curves of NCR's with statistically significant means. Whenever such distribution curves are well graduated and show a normal distribution from the extremes to the mean, we may assume that our sampling is accurate and sufficiently large. The distributions we obtained are apparent from the curves. Hereafter we shall cite only the mean values in the discussion of data.

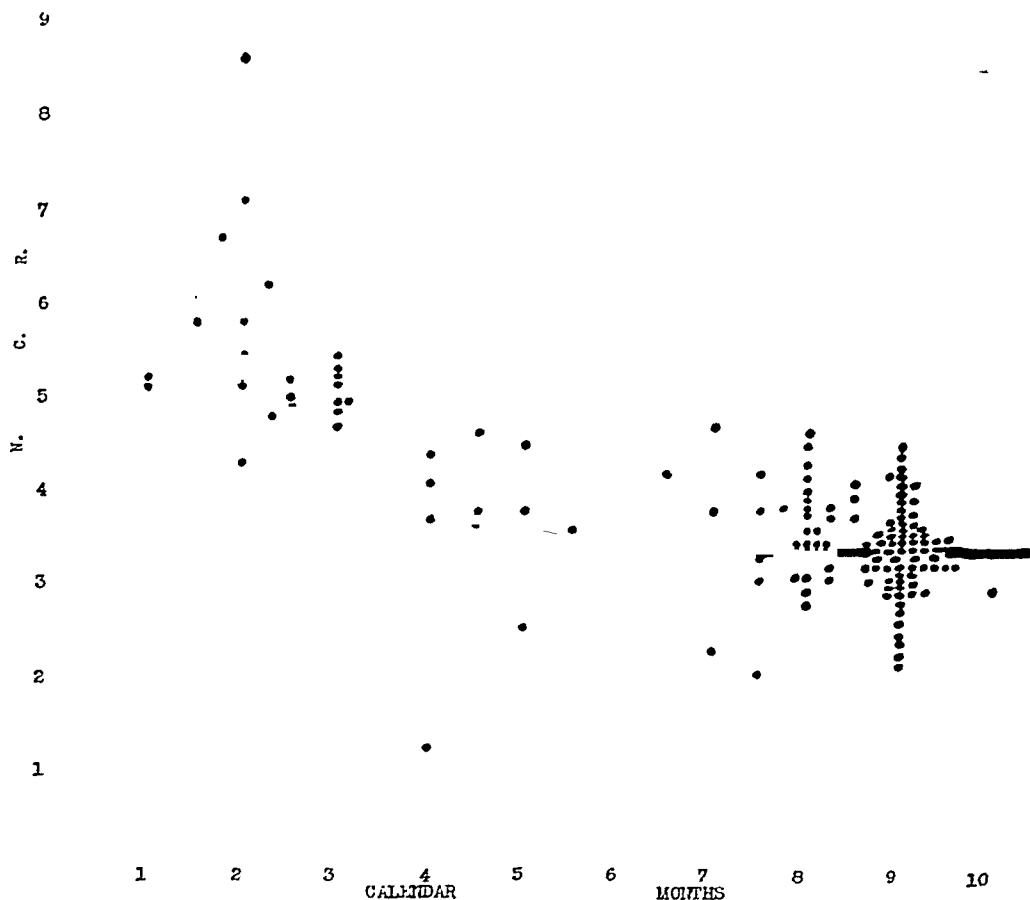


Fig. 1.—Aging curve. Nucleocytoplasmic ratio vs. age.

When the NCR as ordinate is plotted against time as abscissa, the data from all viable placentas describe an aging curve (Fig. 1). This curve is an hyperbola similar to those previously obtained in other tissues by Robertson, Heulin, Le Breton and Schaeffer, and Graff. The original trophoblast is a highly active, invasive, rapidly growing, highly nucleated tissue, obviously with a theoretical NCR of maximal value. Placentas below three months of age approximate 7 per cent; from three to six months the NCR averages 4.5 per cent; and from six months to term the value is about 3.6 per cent.

All complete specimens were weighed after the method of Adair and Thelander, and a curve drawn with the weight as ordinate and age as abscissa. (Fig. 2.) The range was from 30 grams at three months to over 600 grams at term. This corresponds to the generally accepted figures in Williams, DeLee, and other obstetric texts. Ehrenberg and Liebenow have

stated on the basis of a series of 15 placentas that total weight increased markedly in the first seven months of gestation, while dry weight increased even more rapidly. After seven months, total weight continues to increase, while dry weight increases little if at all. Wehefritz, in a similar study of 13 placentas, concluded that both total weight and dry weight increased up to the eighth month, and but slightly thereafter. Our own figures show a more or less constant increment of total weight from month to month, thus agreeing with Ehrenberg and Liebenow but not with Wehefritz. We made no attempt to ascertain dry weights.

A similar curve was plotted with "total nucleic acid" or more specifically, relative active chromatin as ordinate and time as abscissa. Relative active chromatin was computed in each case by multiplying the weight of the placenta in grams by its NCR, and the result by a constant factor to obtain comparable units. (Fig. 2.)

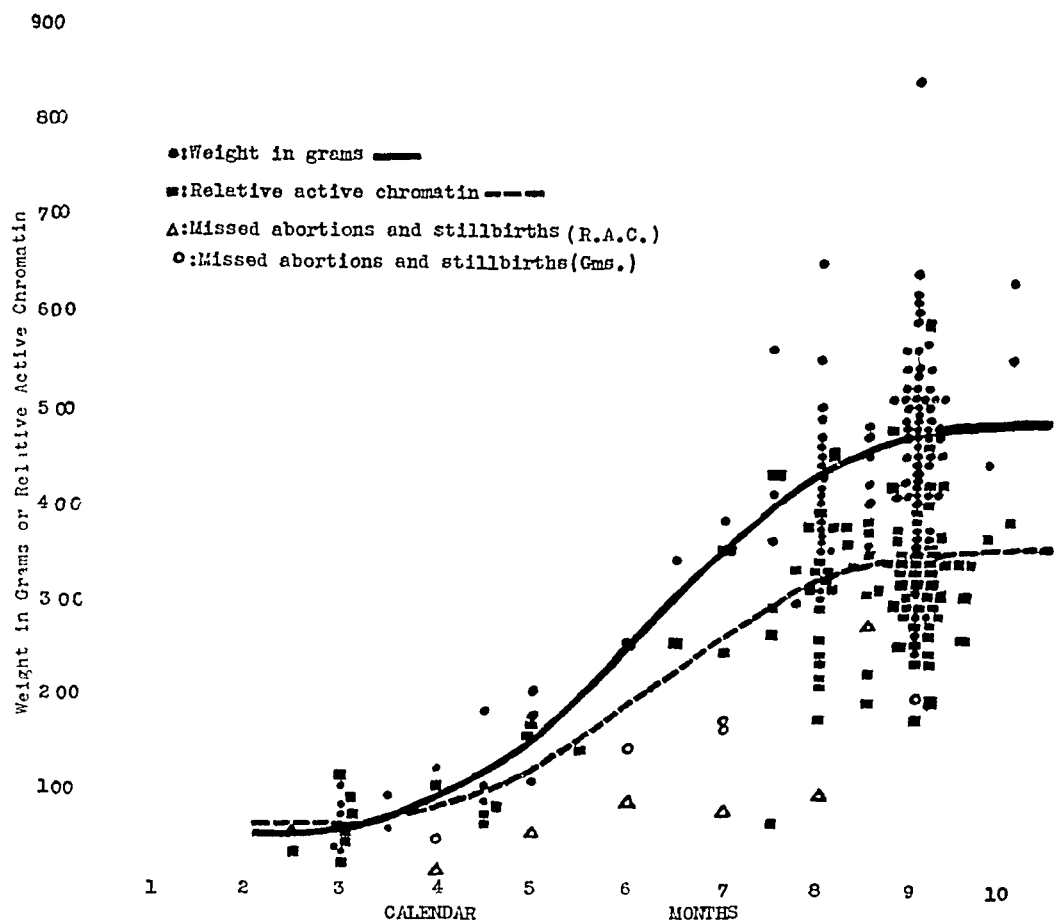


Fig. 2.—Total weight and NCR.

Total weight vs. age of viable placentas—solid circles and line.

Relative active chromatin of viable placentas vs. age—solid squares and broken line.

Total weight vs. age of missed abortions and stillbirths—open circles.

Relative active chromatin vs. age of missed abortions and stillbirths—open triangles.

Both curves correspond to the so-called monomolecular autocatalytic sigmoid growth curve of Robertson, and to the more precisely defined logistic curve of Raymond Pearl—the theoretical and statistical curves of growth.

A mean NCR of 3.27 was obtained from a group of 8 placentas from patients who had undergone normal labor. The mean NCR of a series of 40 placentas from patients subjected to cesarean section without labor and at the same stage in pregnancy was 3.59. These results are suggestive of increased placental aging during labor. (Fig. 3.)

The mean NCR of 13 placentas from severely toxemic patients was 3.29. We must conclude that the severe toxemias do not increase "functional" age of the placenta beyond normal limits. (Fig. 3.)

Placentas from 23 mildly toxemic patients yielded a mean NCR of 3.41. Mild toxemias therefore have no effect upon placental age. Further investigation on the toxemias should establish this more clearly. (Fig. 3.)

As regards missed abortions and stillbirths, however, aging is distinctly increased so that the NCR approaches the figure for pure infarct (0.24 per cent). The statistical mean is 2.76 in a series of 10 specimens. The lowest figures were obtained from the most highly organized placentas,

A mean value of 3.13 was calculated from two overdue organs.

Turning to the onset of labor, this may occur anywhere within a wide range of the NCR, specifically from 1.24 through 4.73. It is obvious that there is *no correlation between* "functional" age of the placenta as expressed by the NCR, and the onset of labor.

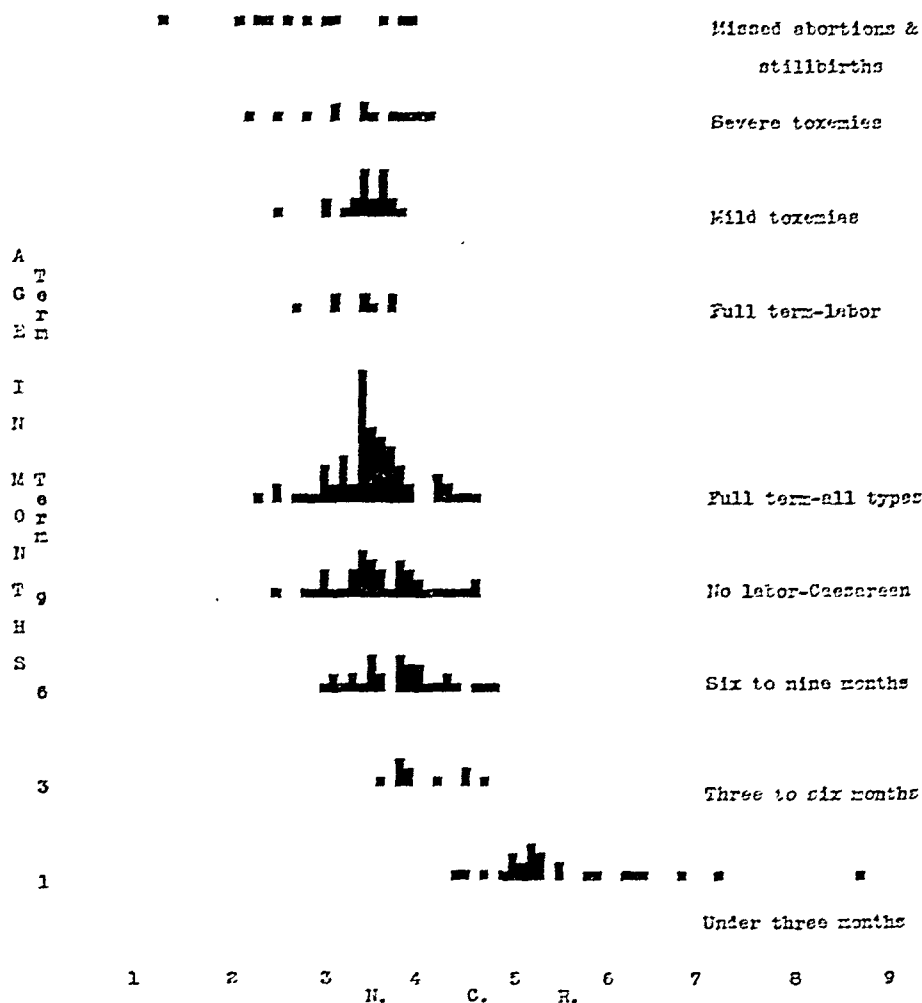


Fig. 2.—Distribution patterns. Age vs. nucleocytoplasmic ratios.

Discussion

Perhaps the earliest recorded theory advanced to explain the onset of labor is that of Hippocrates, who attributed the onset of labor to the inability of the fetus to obtain adequate nutrition after a certain stage of development (Needham). The later recognition of the important role of the placenta in fetal nutrition gave rise to the modern hypothesis that placental senescence initiates labor. Now, if the NCR is pertinent as a measure of placental senescence, and if placental aging does initiate labor, we might expect an inflection in the aging curve at or about the time of labor. No such inflection was found to occur. On the contrary, placental aging is a uniform and gradual process from the fifth month of pregnancy to delivery. Likewise, no particular NCR is characteristic of the onset of labor. Even the onset of labor at term varies considerably, occurring from 2.62 through 3.67 per cent. Similar variations may be observed in any of the other groups of placentas studied.

At the present time predominant opinion favors a hormonal explanation for the onset of labor (Marshall, Snyder, Reynolds, etc.) Since we here confine ourselves to the relation between the placenta and labor, it is fitting that we turn our attention to those hormones apparently produced by the placenta.

Hauptstein has found that the placenta contains large amounts of acetyl choline, greater in the early half of pregnancy than in the latter half. It has been suggested (Reynolds, Walker and Henderson, Chang and Wong) that its known oxytocic effect upon the myometrium may be responsible for the onset of labor. Successful clinical use of acetylcholine has been reported by Bell and Playfair, and Wong and Chang. Chang and Gaddum however, were unable to discover acetylcholine in rabbit placentas. On the other hand, Fontes claims to have prepared strongly oxytocic placental extracts and has found a high concentration of an unknown oxytocic factor in the blood and urine of women in labor. His extracts, however, were thermostable and lipoidal in character. Knaus and Hofbauer have shown that as term approaches the uterus becomes increasingly irritable and more sensitive to pituitrin and other oxytocics. Reynolds, Snyder, and others feel that the changing levels of progesterone and estrogen may act synergistically to cause this increased irritability of the myometrium. Reynolds holds that the placenta may exert a stabilizing influence upon the myometrium, local or endocrine, which declines near term, presumably because of placental senescence.

Furthermore, normal placental age declines from an NCR of 8.6 at two months to 3.6 at term, a decrease of physiologic and chemical activity at term of about two-thirds. At the same time, however, total placental weight increases from 30 to over 500 grams, an increase of more than 1,600 per cent. Even at a lower stage of functional activity such an increase in mass would more than account for the vaunted hormonal production of the placenta. Smith and Smith describe a sudden drop in estrogen and progesterone excretion ten or more days prior to term. If it is assumed that the placenta is indeed the source of these hormones, this decreased excretion might suggest a sudden acceleration in the aging process, with concomitantly decreased production. No such acceleration in aging has been found by us. The possibly increased aging of the placenta during labor, on the other hand, may be attributed to placental ischemia during pains. Woodbury et al. have measured the effective maternal arterial pressure to the placenta during labor and have found it to fall almost to zero during each uterine contraction. This ischemia and coincident anoxemia presumably produce placental damage and aging over the course of time. Theoretically, this factor would be most effective in the longer, least effective in the shorter labors. Further investigation of this point is in progress. Gibbons has speculated upon the manufacture of fetal hormones near term, which hormones are supposedly oxytocic or act as trigger mechanisms at the time when placental senescence presumably lowers fetal nutrition. We are unable to discover any cause for such lowered nutrition within the placenta, since its functional capacity as measured by the NCR remains most adequate.

Adair and Thelander have shown that a high correlation does exist between the weight of the placenta and the weight of the child. Nevertheless, there is on the average always more than enough reserve capacity despite infarction. We may briefly compare the weights of a few placentas with the NCR's obtained (Table II).

TABLE II

	WEIGHT (GM.)	NCR
Placenta 48, labor normal, full-term estimated	499	3.52
Placenta 50, labor normal, full-term estimated	550	3.31
Placenta 60, 8 mo., labor, no infarcts	470	3.75
Placenta 63, no labor, full-term estimated	412	2.85
Placenta 65, no labor, full-term estimated	590	2.98
Placenta 87, sl. labor, ces. 7 mo.	300	4.22

It is apparent that no correlation exists between the weight of the placenta and the NCR.

We may conclude that we have found no evidence that placental senescence as such is directly related to the onset of labor. If any of the afore-mentioned hormonal agents do indeed function as the initiating factors in the onset of labor, and if they are indeed elaborated by the placenta, the cell types responsible for their origin must be relatively few in number, and not demonstrable by our procedure, since no sudden change in NCR is produced.

Browne and Venning, Smith and Smith, Evans et al., and Engle have described a transient rise and subsequent fall of chorionic gonadotropin excretion to a low level after sixty to ninety days of pregnancy. The NCR falls to a comparatively low level at four to five months. Since the NCR is a direct measure of the nucleoprotein content of tissues, and since we know from histological study (Novak; Schaeffer, quoted by Grosser) that the Langhans' cells are relatively absent after four and one-half months, we suggest the possibility that the Langhans' cell layer is responsible for the production of chorionic gonadotropin. At any rate the curve of decline of the trophoblastic NCR parallels the decline of hormonal excretion, pointing once more to the chorionic villi as the source of prolan. Philipp and Huber indirectly, Jones et al. by direct tissue culture methods, have already proved the chorion to be responsible for this hormone.

We do not find that the toxemias have any unusual effect upon the placenta. Others, however, notably Eden, Williams, Young, Bartholomew et al., and Tenney and Parker have found gross and histological changes in the placenta which they consider pathognomonic of placental senescence and toxemia. Bartholomew and Colvin go even farther and suggest that infarct formation with adsorption of toxic breakdown products may be responsible for toxemia. Specifically, the "high" arginine content of the placenta may give rise to autolytic products such as guanidine, which when adsorbed produce toxemia. (Minot and Cutler; Titus et al.) Graff and Graff have shown this argument to be untenable, however, since in fact arginine percentages in the placenta are approximately the same as in all other tissues. Their results, obtained by newer and more accurate methods, discredit the original high figures of Harding and Fort, Ehrenberg and Liebenow, and Wehefritz. Graff and Graff also found no difference in the arginine content of normal and toxemic placentas at term. Krieger, Stander, and Andes have either noted no uniform elevation of blood guanidine in the toxemias, or one which followed rather than preceded hypertension. A rise in guanidine is consequently of no etiological significance (Dexter and Weiss). Hartman, commenting on one of Bartholomew's articles, made the cogent observation that placental infarcts might be caused by the same etiological factor operating to invoke vascular spasm throughout the body in toxemias, rather than that the infarcts caused toxemia.

We have observed no correlation between the number and size of infarcts visually estimated and the NCR obtained. Clements and Williams-Stander similarly state that no correlation exists between the toxemic state and placental infarction. The effect of infarction on the NCR of the placenta may be examined by the relation:

$$\text{where } X \cdot \text{NCR}_{in} + (1 - X) \cdot \text{NCR}_{pt} = \text{NCR}_r$$

X = fraction of infarct
 NCR_{in} = NCR of infarct
 NCR_{pt} = NCR of ideal term placenta (no infarcts)
 NCR_r = NCR found

Thus, in a placenta yielding the value 3.2 per cent, exised infarct was found to have an NCR of 0.24. If NCR_{pl} is then assumed to be 3.6 per cent (the value of full-term no labor placentas), the amount of infarction is computed to be 12 per cent, lowering the NCR by approximately 5 per cent. Williams, Eden, and others have commented on the known enormous reserve functional capacity of the placenta. If half of the above placenta were infarct, the NCR would be 1.72 per cent. A 500-gram placenta, half infarct, with NCR 1.72 per cent, would have the same functional capacity as a 250-gram placenta with NCR of 3.6 per cent and no infarcts.

Since the gross appearance of the placenta was not sufficiently prognostic as regards the NCR, a number of placentas were subjected to histological study. A low correlation was obtained between the NCR and the degree of fibrosis of villi and "syncytial degeneration" (Tenney and Parker). This was not always true, however, suggesting that the histological picture must vary throughout the placenta. Thus, referring to Table III, Patient 1, severe pre-eclamptic, the placental histology was one of extreme fibrosis, some calcification, and some necrosis, the NCR 3.32—practically normal; as regards Patient 3, pathologic report was "normal placenta;" the NCR also 3.32—again a pre-eclamptic. On the other hand, Patient 21, missed abortion 7½ months, placental NCR 2.01, and a microscopic picture of infarction, fibrosis of villi, endarteritis, and what appeared to be syncytial degeneration, no known toxemia existed. Inspection of Table III will furnish many similar examples.

TABLE III

PATIENT	NCR	PATHOLOGIC DESCRIPTION	% INFARCTION (CALCULATED)	CLINICAL TYPE
1	3.32	Extreme fibrosis, some calcification, some necrosis	8.3	Pre-eclampsia
2	2.26	Marked fibrosis and calcification	39.8	Pre-eclampsia and stillbirth
3	3.32	Normal placenta	8.3	Pre-eclampsia
4	3.24	Normal placenta, slight fibrosis	10.7	Cesarean at term
5	3.41	Calcification and fibrosis	5.6	Cesarean at term
6	3.04	Normal, sl. fibrosis. Some syncytial degeneration	16.6	Severe pre-eclampsia
7	3.31	Fibrosis and calcification	8.6	Mild pre-eclampsia
8	3.13	Fibrosis and infarction	13.9	Cesarean at term
9	4.25	Normal placenta		Premature labor 6½ months
10	3.47	Normal placenta with congestion	3.8	Premature labor 7 months
11	3.93	Mature placenta, slight fibrosis		Stillbirth—8 mo.
12	3.44	Mature placenta, slight fibrosis	4.7	Cesarean 8½ mo.
13	2.17	Mature placenta; some fibrosis, some congestion, sl. syncytial degeneration	42.5	Mild pre-eclampsia
14	3.69	Mature placenta and fibrosis, some infarction		Mild toxemia. Cesarean at term
15	3.38	Mature placenta, some fibrosis	6.5	Mild pre-eclampsia
16	2.59	Degeneration of decidua, fibrosis of villi	30.1	Inevitable late abortion 5 mo.
17	4.06	Mature placenta, congestion and infarction, sl. syncytial degeneration		Pre-eclampsia 8 mo.
18	3.98	Mature placenta, congestion and infarction, fibrosis of villi		Pre-eclampsia. Cesarean
19	2.57	Degeneration and chronic inflammation of decidua, fibrosis of villi, infarction of placenta, endarteritis	36.6	Missed abortion 28 weeks
20	4.10	Mature placenta with fibrosis and infarction, some syncytial degeneration		Mild toxemia
21	2.01	Infarction, fibrosis, endarteritis, syncytial degeneration	47.0	Missed abortion 7½ mo.

In Table III is included also the calculated percentage of infarction, which perhaps may be better described as fibrosed functionless placenta. From the functional point of view, those placentas with NCR's of over 3.6 were assumed to have no such tissue. If the child dies in utero the effect on placental "functional" age is more noticeable than survival with toxemia. It is obvious that determination of the NCR eliminates chance selection of pathologic sections because each sample for analysis is an aliquot of the entire placenta. Multiple serial sections of the whole organ would be necessary to give a correspondingly accurate micropathologic picture.

Conclusions

1. Estimation of the NCR reveals that the placenta ages in a uniform and continuous manner, from approximately 8.6 per cent at two months to 3.6 per cent at term.
2. The growth of the placenta conforms to theoretical and statistical laws of growth.
3. The toxemias of pregnancy have no effect upon placental age as measured by the NCR.
4. Death of the fetus in utero lowers the NCR, i.e., causes increased aging, probably by some autolytic process.
5. There is no correlation between placental senescence and the onset of labor.

References

1. Adair, F. L., and Thelander, H.: *AM. J. OBST. & GYNEC.* 10: 172, 1925.
2. Andes, J. E., Andes, E. J., and Myers, V. C.: *J. Lab. & Clin. Med.* 23: 9, 1937.
3. Bartholomew, R. A., and Kracke, R. R.: *AM. J. OBST. & GYNEC.* 24: 797, 1932.
4. Bartholomew, R. A., and Parker, F.: *AM. J. OBST. & GYNEC.* 27: 67, 1934.
5. Bartholomew, R. A., and Colvin, E. D.: *AM. J. OBST. & GYNEC.* 36: 909, 1938.
6. Bartholomew, R. A.: *J. A. M. A.* 111: 2276, 1938.
7. Bell, A. C., and Playfair, P.: *J. Obst. & Gynaec. Brit. Emp.* 44: 470, 1937.
8. Browne, J. S. L., and Venning, E. M.: *Lancet* 231: 1507, 1936.
9. Chang, H. C., and Gaddum, J. H.: *J. Physiol.* 79: 255, 1933.
10. Chang, H. C., and Wong, A.: *Chinese J. Physiol.* 7: 151, 1933.
11. Chang, H. C.: *Proc. Soc. Exper. Biol. & Med.* 32: 1001, 1935.
12. Clements, A. B.: *AM. J. OBST. & GYNEC.* 27: 84, 1934.
13. Cohen, S. L., Marrian, G. F., and Watson, M.: *Lancet* 228: 674, 1935.
14. Colvin, E. D., and Bartholomew, R. A.: *AM. J. OBST. & GYNEC.* 37: 584, 1939.
15. Conklin, E. G.: *J. Exper. Zool.* 12: 1, 1912.
16. Cowdry, E. V., editor: *Problems of Ageing*, ed. 2, Chap. XXVI, Chemical Aspects of Ageing, by C. M. McCoy, Baltimore, 1942, Williams & Wilkins Co.
17. Danforth, D. N., and Ivy, A. C.: Personal communication from D. N. Danforth.
18. De Lee, J. B.: *Principles and Practice of Obstetrics*, ed. 7, Philadelphia, 1939, W. B. Saunders Co.
19. Dexter, L., and Weiss, S.: *Pre-Eclamptic & Eclamptic Toxemias of Pregnancy*, Boston, 1941, Little, Brown & Co.
20. Eden, T. W.: *J. Path. & Bact.* 4: 265, 1897.
21. Ehrenberg, R., and Liebenow, W.: *Pflüger's Arch. f. d. ges. Physiol.* 201: 387, 1923.
22. Engle, E. T.: in *Sex and Internal Secretions*, edited by Allen, E., Danforth, C. H., and Doisy, E. A., ed. 2, Baltimore, 1939, Williams & Wilkins Co., p. 1003.
23. Evans, H. M.: *J. A. M. A.* 104: 464, 1935.
24. Evans, H. M., Kohls, C. L., and Wonder, D. H.: *J. A. M. A.* 108: 287, 1937.
25. Fontes, J.: *Med. contemp.* 48: 61, 1930.
26. Fontes, J.: *Arq. de pat.* 7: 283, 1935.
27. Fraser, J.: *AM. J. OBST. & GYNEC.* 6: 645, 1923.
28. Gibbons, R. A.: *J. Obst. & Gynaec. Brit. Emp.* 34: 739, 1927.
29. Gibbons, R. A.: *J. Obst. & Gynaec. Brit. Emp.* 39: 539, 1932.
30. Graff, S., and Maculla, E.: *J. Biol. Chem.* 110: 71, 1935.
31. Graff, S., Maculla, E., and Graff, A. M.: *J. Biol. Chem.* 121: 71, 1937.
32. Graff, S., and Graff, A. M.: *J. Biol. Chem.* 121: 79, 1937.
33. Graff, S., and Barth, L. G.: *Composition of Tissue Proteins. Cold Spring Harbor Symposia on Quantitative Biol.* Vol. VI, 103, 1938.
34. Grosser, O.: *Frühentwicklung, Einhautbildung und Placentation des Menschen und der Säugetiere*, Munich, 1927, J. F. Bergmann, p. 324.
35. Harding, V. J., and Fort, C. A.: *J. Biol. Chem.* 35: 29, 1918.

36. Hauptstein, P.: *Arch. f. Gynäk.* 151: 262, 1932.
37. Heulin, F. E.: *Australian J. Exper. Biol. & M. Sc.* 6: 59, 1929.
38. Hofbauer, J.: *AM. J. OBST. & GYNEC.* 16: 245, 1928.
39. Hofbauer, J. I.: *J. A. M. A.* 92: 540, 1929.
40. Jones, G. E. Seegar, Gey, G. O., and Gey, M. K.: *Bull. Johns Hopkins Hosp.* 72: 26, 1943.
41. Knaus, H. H.: *J. Physiol.* 61: 383, 1926.
42. Krieger, V. I.: *M. J. Australia* 2: 746, 1934.
43. Le Breton, E., and Schaeffer, G.: *Variations Biochimiques du Rapport Nucléo-Plasmaticque au Cours du Developpement Embryonnaire*, Paris, 1923, Masson & Cie.
44. Marshall, F. H. A.: *Biol. Rev.* 2: 129, 1927.
45. Minot, A. S., and Cutler, J. T.: *Proc. Soc. Exper. Biol. & Med.* 26: 138, 1928.
46. Minot, A. S., and Cutler, J. T.: *Proc. Soc. Exper. Biol. & Med.* 26: 607, 1929.
47. Needham, J.: *Chemical Embryology*, London, 1931, Cambridge University Press.
48. Novak, E.: *Gynecological and Obstetrical Pathology*, Philadelphia, 1940, W. B. Saunders Co.
49. Pearl, Raymond: *Medical Biometry and Statistics*, ed. 3, Philadelphia, 1940, W. B. Saunders Co.
50. Philipp, E., and Huber, H.: *Zentralbl. f. Gynäk.* 60: 2706, 1936.
51. Probstner, A. von: *Endokrinologie* 8: 161, 1931.
52. Reynolds, S. R. M.: *Physiology of the Uterus*, New York, 1939, Paul B. Hoeber, Inc.
53. Robertson, T. B.: *Chemical Basis of Growth and Senescence*, Philadelphia, 1923, J. B. Lippincott Co.
54. Robertson, T. B.: *J. Gen. Physiol.* 8: 463, 1926.
55. Robertson, T. B.: *Australian J. Exper. Biol. & M. Sc.* 5: 47, 1928.
56. Robertson, T. B.: *Australian J. Exper. Biol. & M. Sc.* 6: 33, 1929.
57. Robertson, T. B., and Dawbarn, M. C.: *Australian J. Exper. Biol. & M. Sc.* 6: 261, 1929.
58. Smith, G., van S., and Smith, O. W.: *Surg., Gynec. & Obst.* 61: 27, 1935.
59. Smith, G. van S., and Smith, O. W.: *Surg., Gynec. & Obst.* 61: 175, 1935.
60. Smith, G. van S., and Kennard, J. H.: *Proc. Soc. Exper. Biol. & Med.* 36: 508, 1937.
61. Smith, G. van S., and Smith, O. W.: *AM. J. OBST. & GYNEC.* 33: 365, 1937.
62. Smith, G. van S., and Smith, O. W.: *AM. J. OBST. & GYNEC.* 39: 405, 1940.
63. Smith, O. W., Smith, G. van S., and Schiller, S.: *J. Clin. Endocrinol.* 1: 461, 1941.
64. Snyder, F. F.: *Physiol. Rev.* 18: 578, 1938.
65. Stander, H. J.: *AM. J. OBST. & GYNEC.* 23: 373, 1932.
66. Tenney, B., Jr., and Parker, F., Jr.: *AM. J. OBST. & GYNEC.* 31: 1024, 1936.
67. Tenney, B., Jr., and Parker, F., Jr.: *AM. J. OBST. & GYNEC.* 39: 1000, 1940.
68. Titus, P., Messer, B. S., and McClellan, R. H.: *AM. J. OBST. & GYNEC.* 24: 667, 1932.
69. Walker, F., and Henderson, N. D.: *Canad. M. A. J.* 30: 158, 1934.
70. Wehefritz, E.: *Arch. f. Gynäk.* 124: 511, 1925.
71. Williams, J. W.: *Am. J. Obst., N. Y.* 41: 775, 1900.
72. Williams-Stander: *Textbook of Obstetrics*, ed. 8, New York, 1941, D. Appleton-Century Co., Inc.
73. Wong, A., and Chang, H. C.: *Chinese M. J.* 47: 987, 1933.
74. Woodbury, R. A., Hamilton, W. F., and Torpin, R.: *Am. J. Physiol.* 121: 640, 1938.
75. Young, J.: *J. Obst. & Gynaec. Brit. Emp.* 26: 1, 1914.
76. Young, J.: *J. Obst. & Gynaec. Brit. Emp.* 34: 278, 1927.

TREATMENT OF CARCINOMA OF THE CERVIX BY INTERSTITIAL RADIUM NEEDLES AT THE RHODE ISLAND HOSPITAL*

Supplemental Report

GEORGE W. WATERMAN, M.D., F.A.C.S., AND RALPH DILEONE, M.D.,
PROVIDENCE, R. I.

IN TWO previously published papers by Drs. Pitts and Waterman,^{1, 2} the establishment of the Gynecological Tumor Clinic at the Rhode Island Hospital has been described. The organization of the Clinic and the various steps leading to the adoption of the long-needle technique are discussed. Plates illustrating the method of inserting the needles and the intracervical capsules are shown. Five-year survival rates, mortality and morbidity figures are given.

Since our first publication in 1937, two papers have been published which have particular bearing on the subject of interstitial radiation of carcinoma of the cervix of the uterus. Arneson,³ "The Use of Interstitial Radiation in the Treatment of Primary and Recurrent Carcinoma of the Uterine Cervix," reviews interstitial radiation by a number of writers, including Ward, Healy, Gellhorn, Taussig, Pitts and Waterman. The work of the latter is quite thoroughly discussed as to advantages and disadvantages, and the author makes suggestion as to improvement through a more carefully worked out tissue dosage for each individual patient.

Nolan and Quimby,⁴ in their paper entitled "Dosage Calculation for Various Combinations of Parametrial Needles and Intracervical Tandems," have likewise reviewed the subject of interstitial radiation, and have found strong reasons to feel that improvement in results in radiation of the carcinomatous cervix will come through this means. They have calculated the isodose levels in different parts of the pelvis under certain arrangements of interstitial needles and tandems, including an average arrangement supplied by one of us. Dr. Quimby,⁵ in a personal communication, has assured us that our arrangement gives the most effective distribution so far tested. Nolan and Quimby find some fault, however, with the distribution about the region of the inner os uteri. They have postulated on theoretical grounds what seems to be a better arrangement of needles, which is now being tested at their institution. Both of these articles are very worthy of attention by those interested in interstitial radiation of cancer of the cervix.

It is our purpose in this paper, first, to report ten-year survival rates on 309 cases, 1926 through 1933, previously reported for five-year survivals; second, to add a new series of 198 cases which passed through the Clinic from 1934 through 1938; and third, to review the total of 507 cases, 1926 through 1938.

These series are made up of chronologically consecutive cases seen or examined in the Clinic or in the private practice of the authors. Absolute figures are therefore given. Relative figures are obtained by deducting those cases too advanced to treat, those refusing treatment, or those referred after primary treatment had been given elsewhere.

*Read at a meeting of the Boston Obstetrical Society, Nov. 21, 1944.

Follow-Up

As the five-year survival rate is still the most widely accepted criterion for evaluating results of cancer treatment, the importance of a good follow-up organization is obvious, and is everywhere recognized. Through the faithful and devoted work of our Secretary, Miss Biron, and of the Social Service Department, represented by Mrs. Helen Chalmers and Miss Mary Tognarelli, our follow-up on 309 cases, 1926 through 1933 has been 99.3 per cent, i.e., only two cases lost. Of the total of 507 cases, 1926 through 1938, only two cases were lost 99.6 per cent. As cases not traced are considered as cancer deaths, these statistics have not suffered on this account.

Classification of Cases

The cases in this series have been classified into four clinical stages after the method of Schmitz, except that Stage V is included in Stage IV, as discussed in previous papers.^{1, 2}

The authors have found this classification to be the simplest and most useful.

The number of cases and percentages for each stage are given for the old series (1926-1933) and for the new series (1934-1938), and for the total series (1926-1938), as follows:

STAGE	1926-1933		1934-1938		1926-1938	
	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
I	15	4.8	5	2.5	20	3.9
II	98	31.7	58	29.3	156	30.8
III	110	35.6	98	49.4	208	41.0
IV	86	27.9	37	18.8	123	24.3
	309		198		507	

It is noted that in Stage I, the percentage has decreased slightly in the last series; in Stage II, the percentage is practically the same (31.7 per cent to 29.3 per cent); in Stage III, however, there seems to be quite a significant increase (35.6 per cent to 49.4 per cent); in Stage IV, there is a corresponding decrease (27.9 per cent to 18.8 per cent). We are inclined to interpret these figures as showing the effect of cancer education in the community. This education apparently has had little or no effect in bringing in the early cases. The percentage of later, hopeless cases has dropped, however, about 10 per cent. This is some gain, but shows that education alone is certainly not enough, as it apparently is ineffective in getting the early stages of the disease to the clinic in larger proportions.

Results

Ten-Year Survivals (1926-1933).—Three hundred and nine cases previously reported as to five-year survivals. Table I shows survival rates for five- and ten-year intervals for each clinical stage with number of cases involved, and percentage of each stage to whole group. Of the whole group (309) absolute, 100 cases survived five years, and 69 survived ten years, i.e., 69 per cent of those surviving five years survived ten years; of Stage II, 73.6 per cent; of Stage III, 64 per cent. In Ward's series,⁶ 73 per cent of those surviving five years survived ten years. In this series there were five noncancer deaths before the five-year period ended, and eleven between the fifth and tenth year.

TABLE I. 1926-1933—309 CASES. SURVIVAL RATE BY YEARS 1 TO 10

STAGE	(SCHMITZ)	NO. CASES	5 YR. SURVIVAL %	10 YR. SURVIVAL %
I	(4.8%)	15	(11) 73.0	(7) 46.0
II	(31.7%)	98	(53) 54.0	(39) 40.0
III	(35.6%)	110	(36) 32.0	(23) 21.0
IV	(27.9%)	86	(0) 0.0	
Composite	(100%)	309	(100) 32.3	(69) 22.3
Relative		281	(100) 35.7	(69) 24.5

New Series (1934-1938).—One hundred ninety-eight cases consecutive, absolute, with 100 per cent follow-up. Table II shows survival rates for whole group: absolute 33½ per cent, and relative 36.7 per cent. Twenty-one cases were not treated or not treated primarily by our method. There was one survival in this group. These cases were subtracted in figuring the relative rate.

TABLE II. 1934-1938—198 CASES. SIXTY-SIX FIVE-YEAR SURVIVALS

STAGE (SCHMITZ)	NO. CASES	1 YR.	2 YR.	3 YR.	4 YR.	5 YR.	5 YR. %
I (2.5%)	5	5	4	4	4	4	80.0
II (29.3%)	58	53	45	41	40	38	65.3
III (49.4%)	98	67	41	31	22	21	21.4
IV (18.8%)	37	14	5	3	3	3	8.0
Total absolute	198	139	95	79	69	66	33½
Too advanced—not treated, 21. One case treated elsewhere survived 5 years.							
Total relative	177					65	36.7

TABLE III. 1936-1938—LAST 3 YEARS. FIVE-YEAR SURVIVALS—127 CASES

STAGE (SCHMITZ)	NO. CASES	1 YR.	2 YR.	3 YR.	4 YR.	5 YR.	5 YR. %
I (2.3%)	3	3	3	3	3	3	100.0
II (30.0%)	38	34	29	27	27	26	69.0
III (48.0%)	61	42	30	21	18	18	28.5
IV (19.7%)	25	8	3	3	3	3	4.2
Absolute (100%)	127	87	65	54	51	50	39.3
Not treated (14.3%)	18					1	
Relative (85.7%)	109					49	44.9
18 cases—needles not used as primary method. One treated elsewhere survived 5 years							

In 1933 we began to use deep x-ray therapy as a part of our planned treatment in a few cases. During 1934 and 1935, x-ray was used rather extensively for the first time, but 1934 and 1935 were bad years. It soon became evident that severe reactions were occurring. A better spacing of the x-ray and radium treatment seems to have corrected this fault fairly well, so that in the years 1936 to 1938 inclusive, of the 127 consecutive (absolute) cases or 109 relative cases treated, the five-year results are shown in Table III as 39.3 per cent absolute and 44.9 per cent relative survivals.

TABLE IV. 1926-1938—507 CASES. SURVIVAL RATE BY YEARS 1 TO 5

STAGE (SCHMITZ)	NO. CASES	1 YR.	2 YR.	3 YR.	4 YR.	5 YR.	5 YR. %
I (3.9%)	20	20	19	18	16	15	75.0
II (30.8%)	156	140	113	103	99	91	58.4
III (41.0%)	208	150	103	76	61	57	27.4
IV (24.3%)	123	22	8	6	3	3	2.4
Absolute (100%)	507	332	243	203	179	166	32.7
Not treated (9.7%)	49					1	
Relative (90.3%)	458					165	36.0

In Table IV, the five-year results for the whole group, old and new, 507 cases, are shown.

In such a series as this—507 cases—there are many problems of interest to be investigated and reported on. The scope of the subject is too large to go into great detail about all. Further publication will be necessary to cover some phases of the work.

Renewed Treatment

From 1926 through 1933, 281 cases were treated, 66 cases were retreated (23 per cent), 12 retreated cases survived five years (18 per cent), and 8 of these cases survived ten years (12 per cent).

From 1934 through 1938, 177 cases were treated, 17 cases were retreated (9.6 per cent), 2 cases survived five years or (11 per cent). The percentage of cases retreated has dropped quite definitely in the last series.

Immediate Mortality

Immediate mortality in the 507 cases (1926-1938) has been discussed in our last publication.² We have had no hospital deaths following treatment with interstitial radiation since 1937 in a total of 353 cases treated to Jan. 1, 1945.

Complications Due to Treatment (1934-1938—177 Cases Treated)

The use of radium and x-ray in the treatment of cancer will always carry with it some degree of injury to normal tissues. No one has yet shown how to use these tissue-

destructive agents so that all the cancer cells will be destroyed without damage to the noncancer background. When the cancer is located in a field such as the pelvis, surrounded by tissues rich in blood vessels and lymphatics and areolar tissues, which are known to be particularly susceptible to radiation, bad results in the form of induration going on to necrosis and slough are not uncommon where massive doses are used in too concentrated an area. The various lesions produced by excessive dosage are described by T. F. Todd,⁷ and etiological factors are discussed. Margaret Todd,^{8,9} has described a "paracervical triangle," a zone of tissue about and in back of the cervix particularly susceptible to irradiation damage, whose breakdown is followed by rapid recurrence by "growing down" of cancer from the deeper pelvic lymph structures. Corscaden¹⁰ describes the early and late effects with "final leathery semilunar ridge 6-7 cm. from anus," or anular stricture of rectum. Aldridge¹¹ found that 16.9 per cent of cases treated at the Woman's Hospital developed some injury to the intestine, as shown by routine x-ray on all patients. Our experience, using interstitial long parametrial needles, is therefore of interest and should be given.

In previous publications we have reported our fistula incidence as 7.9 per cent for the whole series (1926-1938) of 480 cases treated. In the last 177 cases (1934-1938) 15, or 8.4 per cent developed fistulas. Of these 15, five were vesicovaginal fistulas; four were rectovaginal fistulas. Of these fistulas, three rectovaginal closed spontaneously; one vesicovaginal closed spontaneously; one large vesicovaginal fistula was closed surgically. One patient, a diabetic, died of sepsis after attempted closure of a large vesicovaginal fistula five years after original treatment, and one died after surgery for closure of ileovaginal fistula. Of the 15 patients with fistulas, three lived five years or more.

No Stage I cases developed fistulas. There were five cases in Stage II, eight cases in Stage III, and two cases in Stage IV which developed fistulas after treatment.

The incidence of fistula does not tell the whole story, however. Lesions of the bladder mucous membrane, from mild erythema through edema, thickening, and ulceration due to endarteritis may follow treatment. These lesions usually heal but often leave a smooth, pale, somewhat thickened membrane with underlying scar tissue containing telangiectatic vessels. Bleeding and ulceration several years after treatment from this type of lesion may occur. Injury to the ureters with ulceration or cicatricial stenosis has occurred with resultant hydronephrosis and hydronephrosis.

In this series of 177 treated cases, we have had the following such lesions develop.

1. Three cases had bleeding from bladder, due to trophic ulcer or telangiectatic vessels.
2. One case, with large vesicovaginal fistula previously reported, developed pyelonephritis seven years after treatment and died.
3. One patient (post partum) had severe bladder ulcer and infection of bladder with resultant pyonephrosis. She had right nephrectomy ten years after treatment and left nephrostomy twelve years after treatment. She is now alive and in good condition, but wears a nephrostomy tube.
4. One patient had obstructed ureter on right side with resultant pyonephrosis necessitating nephrectomy. She is now alive and well after eight years.
5. Two cases had some degree of hydronephrosis due to ureteral stricture. They were treated by dilatation of ureter without operation and are alive and well.
6. Three patients had bladder ulcer: of these, one died ten months, one, one year, and one, two years, after treatment.

In all, therefore, we have had 11 cases which developed urinary tract lesions other than fistulas. If we add to these 11 the 10 vesicovaginal fistula cases, we get 21 injuries, or 11.8 per cent, in 177 cases.

As we have not adopted the practice of having routine x-ray examinations of rectum and sigmoid on all cases but have employed these diagnostic measures only where symptoms or objective signs have indicated their need, we have doubtlessly missed a few of the milder lesions and our incidence of intestinal damage will doubtless be lower than that of those who use x-ray examination on all cases, e.g., Aldridge's series of 142 cases with 16.9 per cent incidence of intestinal injury.

In going over our records we found the following intestinal complications, ranging from simple proctitis with tenesmus and perhaps some bleeding, through larger ulceration, fistula formation, or perforation into peritoneum: (1) 10 cases of bleeding and tenesmus, (2) one large rectal ulceration thought mistakenly to be cancer and resected, (3) one case of necrosis of the transverse colon with perforation which was repaired followed by recovery of patient, (4) one case of ulceration and perforation of the rectosigmoid into the peri-

toneum, with peritonitis resulting in death, (5) one case of intestinal obstruction which occurred about one year after treatment for cancer of the cervix complicated by a large fibroid. This case died without operation—no autopsy.

In all, 14 cases developed intestinal lesions not including fistulas (8 per cent). If the 10 intestinal fistulas (9 rectovaginal and 1 ileovaginal) are included, we have an incidence of 24 in 177, or 13.5 per cent intestinal injuries following treatment.

Effect of Age on Five-Year Survival Rates

Because it is usually believed that younger people have a graver prognosis with carcinoma of the cervix as with cancer elsewhere in the body, the authors were interested to go through these cases in order to see what effect age has had on prognosis. We have based our conclusions on five-year survival rates.

TABLE V. 1926-1938—507 CASES. SURVIVAL RATES BY AGE GROUPS

AGE (YR.)	CASES (NO.)	5-YEAR SURVIVALS	
		(NO.)	(%)
30 and under	21	9	42.5
31-35	33	13	39.0
36-40	64	25	39.0
41-45	58	20	35.0
46-50	82	29	34.5
51-55	77	26	34.0
56-60	76	20	26.0
61-65	35	15	43.0
66-70	30	6	20.0
71-75	18	1	5.0
76-80	10	0	0.0
Over 80	3	1	33.3
Total	507	165	32.7
45 and under	176	67	38.0
46 and over	331	98	29.5

As shown in Table V, we have divided our cases into five-year age groups, placing those under 30 and those over 80 in single groups. The five-year survival numbers and rate per cent are shown in separate columns. The results in this series show that more of the younger groups survived five years, the best results being in the 21 cases under 30 years of age, or 42.5 per cent. Of course this is too small a number on which to base too serious conclusions. If the cases are divided into two groups, first those over 46 years and second those 45 years and under, we find that 176, or 34.7 per cent, of all of the cases were 45 years or under, and that 67 or 38.0 per cent, survived five years. In the older group, 46 years or over, there were 331 cases, 65.3 per cent of all cases, with 98 survivals, or 29.5 per cent. These figures certainly are significant and indicate a definitely better prognosis for the younger group in this series.

If the cases are divided into clinical stage groups and each stage into age groups 46 years and above and 45 years and below, we find that in Stage I, the age groups are about equally divided, 45-55, but that with each increase in spread of disease as shown by stage, that the proportion of the younger group becomes less, and that of the older more. This can mean only that younger women came in for treatment sooner, and with less involvement, and consequently had a better prognosis in this series. These figures are quite different from those reported from the Barnard Free Skin and Cancer Hospital by Norman Hall,¹² who found in a study of the case histories of 57 patients with cancer of the cervix, 30 years old or younger, that the prognosis was extremely poor in the young woman; that these younger women do not present themselves early for treatment but only when the disease is far advanced.

Dosage

In this series we thought it might be of interest to try to reach some conclusions as to dosage and its effect as measured by the five-year survival rate. As our only estimate of dosage for a given case is the number of milligram hours given, we must recognize a certain inaccuracy. However, certain factors have been quite constant, e.g., the intrauterine 20-mg. capsule and the time element. Variables have been the number and strength of the needles, and the arrangement of the needles, as well as the use of x-ray therapy.

We have never used any so-called standard pattern, but have individualized each treatment at the operating table, trying to place the needles about the growth according to the

direction in which we found it extending. We have used from six needles in small lesions, to sixteen in large ones. We have never believed that any one arrangement of needles would be cancerocidal for all growths. We feel that there is too much variability (1) in the radio-sensitivity of the tumors, (2) in the blood supply, condition of arterioles and of lymphatics which effect the resistance of the normal tissues, to allow of too exact an estimate of the amount of dosage to be employed. We have felt that the strength of the argument for interstitial small sources, widely separated, lay in the fact that dosage could be adjusted to the individual growth in the most flexible manner.

This variability in our method of inserting few or many needles, in accordance with what we saw or could feel digitally at operation, is reflected in the dosage table arranged by dividing the cases treated into groups per 1,000-mg. hour dosage. (See Table VI.)

TABLE VI. 1926-1938. STAGE II.

DOSAGE DISTRIBUTION WITH FIVE-YEAR SURVIVAL					
MG. HR.	NO. CASES	5 YR. S.	5 YR. S. %	RA. ALONE	X-RAY BEFORE OR AFTER
1 M+	9	0	0.0	6	0
2 M+	9	8	88.8	5	4
3 M+	15	11	73.0	14	1
4 M+	12	6	50.0	11	3
5 M+	11	8	72.7	4	5
6 M+	30	25	83.0	19	13
7 M+	15	6	40.0	9	7
8 M+	31	18	58.0	16	15
9 M+	20	8	45.0	13	5
10 M+	4	1	25.0	2	2
	156	91	58.3	99	55

Stage II: We have taken our 156 cases, Stage II, and divided them according to dosage of radium element, i.e., milligram hours. The number of cases receiving increasing amounts of radium are shown with their five-year survival rates. Those cases having smaller lesions apparently received smaller dosage and yet gave high percentages of survival. There are relatively few in these groups. One notes a group of 41 cases which received between 5,000 and 7,000 mg. hours with 33 five-year survivals, or 80.5 per cent, and might draw the conclusion that the optimum dosage for the average Stage II (Schmitz) tumor, treated by this method, lay between these two levels.

TABLE VII. 1926-1938. STAGE III.

DOSAGE DISTRIBUTION WITH FIVE-YEAR SURVIVAL					
MG. HR.	NO. CASES	5 YR. S.	5 YR. S. %	RA. ALONE	X-RAY BEFORE OR AFTER
1 M+	10	1	10.0	6	4
2 M+	11	6	54.0	8	3
3 M+	15	4	26.0	9	6
4 M+	24	11	45.8	14	10
5 M+	17	7	41.0	7	10
6 M+	33	6	18.0	9	24
7 M+	31	8	25.8	8	23
8 M+	44	12	27.2	11	32
9 M+	16	4	25.0	9	9
10 M+	4	0	0.0	0	4
	205	59	29.2	81	125

A similar table, showing dosage in 205 Stage III lesions shows the same wide variations, 10 cases receiving less than 2,000 mg. hours, and 4 cases over 10,000 mg. hours. The groups between 4,000 and 6,000 (41 cases with 18 survivals in five years) seem to point to this dosage as most favorable, i.e., 44 per cent five-year survival.

It is noted that, as the higher dosage levels were attained, more x-ray therapy was combined. It would seem, from a study of these tables, that we were probably overtreating some of the larger lesions and that the employment of fewer needles or needles more widely spaced might improve our results, particularly where x-ray therapy is combined with radium. These tables seem to show that overtreatment can spoil good results as easily as under-treatment.

The authors hope to make a more careful analysis of dosage, particularly as it is affected by x-ray treatment, at a later time.

Other Facts of Interest

In the total series, there were 14 cases of adenocarcinoma, an incidence of 2.7 per cent (14:507). The survival rate of 20 per cent is lower than that for the general series. There were 28 cases of cervical stump cancer, of which 4 were adenocarcinoma and 24 squamous cancer. The five-year survival rate of 33 per cent was about that of the whole series.

There were 9 cases of cancer of the cervix complicating pregnancy. Of these, two were discovered in the first trimester with 2 five-year survivals; five were in the second trimester with 2 five-year survivals; none in the third trimester; and two in the immediate postpartum period with 1 five-year survival. There were in all, 5 out of 9 (55 per cent) five-year survivals in this small series. A further more detailed report is to be given in a later publication.

In this whole series of 507 cases, 8 cases developed bone metastases—the greater trochanter of the femur, the spinal vertebrae, the ileum, and the pubis being involved; 7 cases developed generalized metastases; and 10 cases developed primary cancers in a second organ.

Summary

Ten-year survival rates for the series (1926-1933) previously reported for five-year rates are given.

An additional series of 198 cases are reviewed for mortality and morbidity incidence.

An improvement in results in the last three years (1936-1938) in 127 cases is shown.

The effect of age on extent of growth when first seen (clinical stage) and on prognosis (five-year survival rate) is shown.

The incidence of adenocarcinoma, carcinoma complicating pregnancy, bone metastases, generalized metastases, and cancer primary in a second organ is given for this series.

Conclusion

The good results previously reported with the use of interstitial long platinum needles of low intensity are maintained in this series, and, with the added use of x-ray therapy in the last consecutive 109 treated cases, are definitely improved.

Through a more carefully worked out distribution and spacing of the radium sources, as suggested by a study of dosage and five-year survival rates, it is hoped that these results may be further improved.

The authors wish to express their sincere appreciation to Dr. Herman C. Pitts, former Chief of this Service, for his continued interest in this work and for permission to include his private cases in this report.

References

1. Pitts, H. C., and Waterman, G. W.: *Surg., Gynec. & Obst.* 64: 30, 1937.
2. Pitts, H. C., and Waterman, G. W.: *Am. J. Roentgenol.* 43: 567, 1940.
3. Arneson, A. N.: *Radiology* 30: 167, 1938.
4. Nolan, J. F., and Quimby, E. H.: *Radiology* 40: 391, 1943.
5. Quimby, E. H.: Personal communication.
6. Ward, George G. and Sackett, N. B.: *J. A. M. A.* 110: 323, 1938.
7. Todd, T. F., *Surg., Gynec. & Obst.* 67: 617, 1938.
8. Todd, Margaret: *Brit. J. Radiol.* 11: 809, 1938.
9. Todd, Margaret: *Brit. J. Radiol.* 14: 23, 1941.
10. Corsecaden, J. H., Hasaback, H. H., and Lenz, M.: *Am. J. Roentgenol.* 39: 871, 1938.
11. Aldridge, A. H.: *AM. J. OBST. & GYNEC.* 44: 833, 1942.
12. Hall, Norman: *Canad. M. A. J.* 43: 362, 1940.

COMPLETE ABDOMINAL HYSTERECTOMY*

Impressions Based on 135 Cases

ROY W. MOHLER, M.D., AND EDWARD H. BISHOP, M.D., PHILADELPHIA, PA.

(From the Gynecological Service, Jefferson Hospital and Philadelphia Lying-In, Pennsylvania Hospital)

COMPLETE hysterectomy by the abdominal route has become an increasingly popular procedure in the past two decades, and more gynecologists are finding indications and advantages for it. It is our purpose in this presentation to discuss some convictions which we have acquired in regard to the complete hysterectomy done by the abdominal route. These convictions are based on a study of 135 operations done at the Jefferson Hospital and at the Philadelphia Lying-In Hospital over a relatively short period of time and after a definite technique had been developed. Most of the operations have been done by the senior author, and in all instances the senior author was personally responsible for the patients used as the basis for this presentation.

The reason for reporting 135 cases has been to use a series of cases which have been operated upon with similar technique and surgical personnel, thereby avoiding an important variable in the management of these patients. In some instances, the house officer or the junior member of the staff did the actual surgery, but identical technique was used in each of the cases in this series.

Supravaginal hysterectomy has been a standard gynecologic procedure for many years. It was one of the early types of abdominal operations and holds a very high position among operations as far as cure or relief of the patient or her symptoms are concerned. Supravaginal hysterectomy has been utilized very generally as the procedure of choice, and has been very successful in the cure of symptoms produced by such lesions as myomata uteri, adenomyosis uteri, functional uterine bleeding, partial descensus of the uterus, pelvic inflammatory disease, endometriosis, endometrial polyps, and benign uterine adnexal disease. In all of these conditions it was thought advantageous or not disadvantageous to conserve the cervix uteri. Some of the advantages which are attributed to supravaginal hysterectomy have been the simplicity of the technique, slight blood loss, absence of postoperative morbidity, and very low mortality. Beside these immediate advantages, great importance has been ascribed to the cervix uteri as a fundamental structure in the human female. The preservation of the cervix uteri has been thought to be necessary to maintain normal support of the vaginal vault and bladder, to maintain normal vaginal secretion, and to prevent shortening of the vagina.

Physiologic observations and knowledge accumulated in the last two decades have allowed for tremendous extensions of surgical procedures, and what was considered adequate and successful surgery twenty years ago does not apply today. This statement applies to the surgery of all systems of the body and, of course, it applies to the surgery undertaken by the gynecologist. The fact that complete hysterectomy is a more difficult and dangerous operation to accomplish without adequate experience has no right to influence our judgment as to its

*Read at a meeting of the Philadelphia Obstetrical Society, Jan. 4, 1945.

merits. It is up to the gynecologist to train himself to overcome the technical difficulties and do the operation that is to the patient's ultimate advantage.

With these facts as a basis, we have studied this series of complete abdominal hysterectomies and wish to discuss our observations and results.

Technique

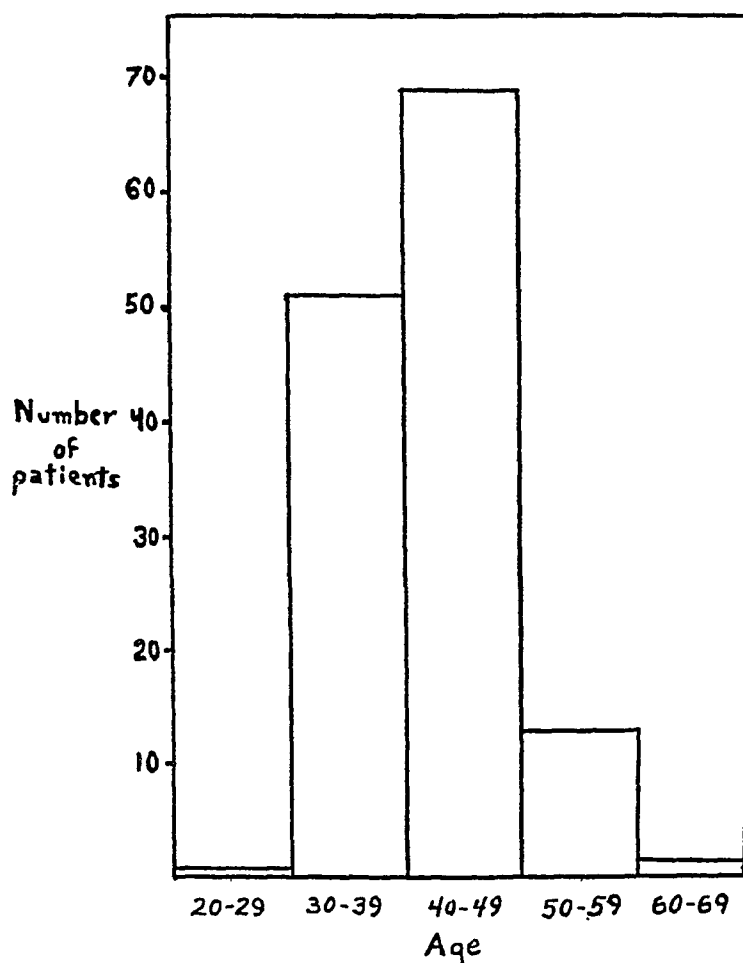
The technique which was used in performing the operations used as a basis for this presentation is as follows: The vagina is cleansed by scrubbing as in many gynecologic procedures. This scrubbing is followed by the use of some antiseptic, preferably a 1:1,000 aqueous solution of zephiran. This is done in the operating room and should be followed by any necessary vaginal plastic procedure. A self-retaining catheter is placed in the bladder and is allowed to remain there for seventy-two hours following operation. This allows for continuous drainage of the bladder and was done originally because we thought injuries to the bladder and the ureters could be recognized early if they occurred. Fear of injuring the bladder and ureters has proved an unnecessary indication for the use of the continuously draining catheter, but we have continued to use it because we think it decreases the necessity for nursing care. It is also our impression that the catheter avoids immediate postoperative bladder dysfunction and immediate postoperative morbidity due to it.

The technique of the abdominal complete hysterectomy is really an extension of the technique which we ordinarily use for supravaginal hysterectomy. The abdomen is opened in the routine manner, and when possible a self-retaining retractor is used to facilitate exposure of the abdominal content. Ordinarily, we try to avoid the use of abdominal packs, but sometimes they are necessary. The uterus and its adnexa are entirely freed, and mobilized as completely as possible before beginning the actual operation. Except when malignancy of the urine body or pyometra is suspected, a large tenaculum forceps is placed in the body of the uterus to facilitate manipulation of the uterus by traction and thus expose the various supporting and fixed structures connected with the uterus. The round ligaments are ligated and separated from the uterus, and the bladder peritoneal flap is developed and separated from the uterus for a short distance. The ovarian vessels are ligated and separated from the uterus. All reflux bleeding is controlled by clamps on the uterus or its adnexa, but no clamps are used before placement of the ligatures. The broad ligaments are separated from the side of the uterus almost down to the position of the internal os of the cervix. At this point the uterine vessels are exposed and a ligature is placed around them, and a clamp is placed above the ligature to control the reflux bleeding from the uterus. The uterine vessels are cut directly across above the ligature and then the vessels are dissected from the side of the uterus. Usually about $1\frac{1}{2}$ centimeters of the uterine vessel is exposed by cutting through the parametrium before any bleeding occurs. A second, and sometimes a third, ligature is then placed around the uterine vessel, and further dissection of the vessel is made. The fascia which lies over the cervix is then separated from the cervix, and the bladder is separated from the vagina as far as necessary. With this procedure the ureters drop well out of the way and there need be no fear for their injury. After partial separation of the uterine vessel on both sides, the uterosacral ligaments are exposed and ligated and separated from the uterus, at which point mobilization of the uterus is usually complete. After complete control of the circulation to the uterus, the whole structure is separated from the vagina with a knife, cutting perpendicularly to the axis of the vagina. When the uterus has been amputated from the vagina, there may be very slight blood loss from the vaginal cuff. All structures are finally re-ligated, and then the vaginal canal is closed with a continuous suture of fine catgut placed very lightly and in such a way that the vaginal mucosa is inverted into the canal. We have been very careful to avoid the use of through-and-through sutures in the vaginal canal. It is our impression that proper closure of the vagina is one of the very important details of the operation as we do it. The round ligaments and the utero-ovarian or infundibulopelvic ligaments, the perivaginal fascia and the uterosacral ligaments are fixed to the vault of the vagina. This supports the vault of the vagina and helps somewhat to cover the exposed pelvic surfaces. All raw surfaces in the pelvis are covered with peritoneum and only one knot is exposed to the peritoneal cavity. We prefer to use No. 0 or smaller catgut sutures throughout the procedure, and we have the impression that this is good surgical practice.

The anesthetic used for most of these cases has been continuous or fractional spinal with special consideration for small doses. In the series of cases which we are using as a

basis for this discussion, 2 c.c. of 5 per cent procaine hydrochloride solution in immediately withdrawn spinal fluid was used as the initial dose and 1 c.c. of the solution was used as necessary to supplement the original dose. Usually, 5 or 6 c.c. of the solution were necessary to complete the operation, or a total of 250 to 300 mg. procaine hydrochloride. This type of anesthetic gave good and adequate relaxation, prevented dangerous depression of the blood pressure, and allowed for careful and deliberated technique. The time, trauma, and immediate blood loss sustained for these complete abdominal hysterectomies were not remarkably greater than for any other type of abdominal operation. The immediate effects of the operation on the patient are surprisingly slight and would seem to be no greater than occurs with any major gynecologic procedure. We are convinced that if a definite technique is undertaken and learned and executed often enough to be carried out expeditiously, the operation can be done safely and carefully with no extra hazard to the patient. With these points in mind, we have studied our series of cases.

TABLE I. AGE OF PATIENTS



There was only one patient in this series under 30 years of age, but, because of our experience, we feel that there is no real objection to removing the cervix in young women when no endometrium can be conserved, regardless as to whether the adnexa must be removed or not. This statement is made deliberately and implies that the cervix per se serves no useful purpose in an individual who must have all of the endometrial tissue removed. We also feel that the cervix is very definitely responsible for some minor gynecologic disturbances if it is retained.

The extent of the operation and the additional surgical procedures are shown in Tables II and III. These are shown with the idea of demonstrating that routinely the disposition of the uterine adnexa is made without regard to the conservation of the cervix, and it is our practice to conserve the uterine adnexa in all patients up to the age of 50 years, when they appear normal and when there is no indication in the patient's history of endocrine imbalance. The table showing the number of additional procedures indicates that these can be accomplished without undue danger to the patient and can fulfill the concept that gynecologic operations are often multiple operations accomplished with the idea of completely reconstructing

the genital organs and relieving the patient of her symptoms referable to the genital tract. Here again, we feel that the conservation of the cervix need not have been considered and the patient is better for its removal.

TABLE II. TYPE OF OPERATION

Total hysterectomy, conservation of adnexa	32
Total hysterectomy, partial removal of adnexa	36
Total hysterectomy, complete removal of adnexa	67

TABLE III. ADDITIONAL SURGICAL PROCEDURES

Dilatation and curettage	14
Appendectomy	29
Vaginal plastic	19

TABLE IV. MORBIDITY

Postoperative reaction	23
Urinary infection	12
Wound infection	4
Pyelitis and retained sponge in vagina	1
Thrombophlebitis	1
Perirectal abscess	1

Table IV shows the temperature morbidity following this series of operations. The incidence of 23 postoperative reactions may seem high and actually indicates an unexplained cause for temperature reaction for the seventy-two hours immediately following operation. Temperature reactions occur frequently following any extensive operation through the peritoneal cavity. The explanations for it are numerous. Many explanations are hypothetical, and others have a real basis. A small rise of temperature following an operation need give the physician no particular concern and does not seem to retard the patient's ultimate and complete recovery. The incidences when the cause for temperature morbidity was definite are shown on the table and the number is about what one would expect following any extensive surgical operation.

In one patient a ureter was severed while operating. The accident occurred during the release of an adherent adnexa and after immediate catheterization and repair of the ureter, a complete hysterectomy was done. There were no known bladder injuries. There was one intestinal injury which occurred when an adherent adnexa was freed. There was no immediate mortality in any of these cases and there has been no immediate mortality in our experience with complete hysterectomy.

TABLE V. LENGTH OF HOSPITALIZATION FOLLOWING OPERATION

	DAYS
Shortest	11
Longest	43
Average	15.1
Mean	14

In this series of cases (Table V) the average number of hospital days following operation before discharge from the hospital was 15.1 days. The shortest stay in the hospital following operation was 11 days and the longest stay was 43 days. We believe that 14 days is the optimum period of hospital stay for all patients having major gynecologic operations, and this is not changed because of the operations which we are reporting.

TABLE VI. INDICATIONS FOR OPERATION

Fibromyomas	67
Fibromyomas and adnexal pathology	29
Fibromyomas and vaginal relaxation	16
Endometriosis	8
Functional bleeding	7
Descensus	4
Carcinoma of fundus	3
Carcinoma of tube	1

Carcinoma of the cervical stump has been used as the chief indication for complete hysterectomy. (Table VI.) Carcinoma of the cervical stump has been observed 21 times in a series of 541 cases of carcinoma of the cervix observed and reported by Dr. Lewis C. Scheffey from the Jefferson Hospital. The importance of the retained cervix as a cause for minor gynecologic disturbances has not been emphasized as an indication for complete hysterectomy. These disturbances which have seemed important to us are endocervicitis or diseased cervix, leucorrheal discharge, prolapse of the cervical stump, and the absence of normal vaginal biology.

Follow-up Observations and Discussion

In this series of cases which have had complete hysterectomy by the abdominal route, we have been interested in four considerations: First, granulations in the vault of the vagina; second, support of the vaginal vault; third, shortening of the vagina; fourth and finally, the development of normal vaginal biology.

Granulations in the vault of the vagina have occurred in 27 per cent of our patients. These areas have never been extensive and have usually occurred at the lateral angles of the vaginal incision. They have been managed by curetting the granulation tissue a few weeks following operation. If these areas of granulation are not destroyed, it is our impression that they will produce an abnormal vaginal flora and consequently a leucorrheal discharge. In our experience, they have not been a troublesome problem, but they should and can be prevented with proper attention to closure of the vaginal vault. We think the incidences of their occurrence have become less as we have learned to close the vault of the vagina more meticulously.

The support of the vaginal vault is not dependent upon the presence of the cervix. This statement is proved by the fact that vaginal hysterectomy is the most successful treatment for prolapse of the uterus and vaginal eversion. This detail is considered in our technique and is accomplished by fixation of the paravaginal fascia, the round ligaments, the ovarian pedicles, and the uterosacral ligaments to the vault of the vagina. Prolapse of the vault of the vagina has not occurred in this series of cases, and theoretically we believe that it should not occur when consideration is given to fixation of the vaginal vault.

Vaginal Shortening

Vaginal shortening because of the removal of the cervix was observed once in this series of cases, and in some instances it was our impression that the vagina was lengthened. In evaluating the length of the vagina, one must appreciate that the personal equation is a variable factor and that there is normally a great variation in the length of vaginas. It is difficult to understand how the operation of complete hysterectomy could influence very greatly the length of a structure which has such individual variations. It does not seem logical to assume that removal of the cervix without vaginal repair could alter the length of the vagina sufficiently to interfere with complete or satisfactory coitus.

Vaginal Biology

We have been interested very much in the biology of the vagina following complete hysterectomy. Our studies of this problem have not been completed and some of our concepts are hypothetical, but it is our impression that normal vaginal biology exists after complete hysterectomy and that the climacteric occurs at its normally expected time when the ovaries have been conserved. This conclusion is based on the examination of a great many vaginal smears following complete hysterectomy, with conservation of the ovaries, and

before and after the use of extrogenic substances when the ovaries have been removed. Much importance should be ascribed to this conclusion, and it would seem that the value of complete hysterectomy as a standard and acceptable procedure can depend very largely upon this conclusion.

Conclusion

In this presentation we have discussed the merits and impressions secured from an experience of 135 complete abdominal hysterectomies with a similar technique and by the same personnel. It was thought that the deductions drawn from this experience might be worth presenting.

The supravaginal hysterectomy holds a definite and respected position in surgery and should be used when the opportunity has not been available to standardize a technique for complete hysterectomy and in other instances where some of the endometrium and adnexa can be conserved.

First, the cervix per se is not a very important structure when no endometrium can be conserved, and it is responsible for some minor gynecologic morbidity following operation.

Second, the mortality from complete abdominal hysterectomy should not be greater in a large series of cases than other gynecologic procedures. The operation is difficult, but in the light of advancement in surgical technique, it is not more difficult than other accepted surgical procedures. In this series of cases there was no mortality.

Third, the immediate temperature morbidity is not more than any other gynecologic procedure. Theoretically, it should be lower except in cases where pelvic inflammation accompanies the indication for operation.

Fourth, we think the remote morbidity is less following complete hysterectomy and have outlined briefly some of our reasons for this conviction.

Finally, we believe that complete hysterectomy is a complete operation that should be utilized by well-trained gynecologists, and as one's experience with it grows, its merits will become obvious and impressive.

Discussion

DR. CHARLES A. BEHNEY.—It was surprising to find, in Dr. Mohler's series, only 19 plastics in 135 instances of total hysterectomy, most of the women being over 50 years of age. In this connection I should like to recommend Meigs' technique for dealing with vaginal relaxations in patients requiring total hysterectomy. Instead of repairing the vaginal walls before doing the hysterectomy, Meigs performs the total hysterectomy first, cutting a V-shaped section out of the anterior vaginal cuff. If the patient's condition is good after the hysterectomy, she is put in the lithotomy position for repair of the vaginal relaxation. The advantage in performing the operations in this, the reverse of the usual order, is that the more shocking and hazardous procedure is done first. If the patient's condition is questionable after the total hysterectomy, the plastic work can be postponed for seven to ten days. Usually there is no contraindication to completion of the vaginal work at the same time.

In performing the operations in this order, the operator is surprised to find that in drawing the anterior peritoneal flap over the vaginal cuff, after excising the V-shaped portion of the anterior vaginal wall, he has shortened the anterior vaginal wall to such an extent that further plastic work on it is unnecessary. The posterior wall is also shortened but perineorrhaphy will be needed in most instances. Large rectoceles will also require repair. By doing the surgery in this order, one avoids a long, sometimes bloody vaginal operation which leaves the patient devitalized and sometimes shocked before the more difficult abdominal surgery is begun.

DR. MOHLER (closing).—I cannot concur in Dr. Nicholson's viewpoint of not scrubbing the vagina before complete hysterectomy. The primary reason should be to remove the collected debris from the vagina. My enthusiasm for complete hysterectomy is due to the

fact that I have been interested in the management of leucorrhœal discharges, and often, following supravaginal hysterectomy, the patient has a leucorrhœal discharge. If one removes cervixes more often, fewer patients will complain of a leucorrhœal discharge. We do not know how to manage vaginal discharges entirely successfully and it has been my concept that the cervix is very often responsible for the discharge. It is also my impression that most leucorrhœal discharges have their genesis in a diseased cervix or some type of endocrine imbalance, and I think a diseased cervix is difficult to treat. We have good results with the management of some patients with endocrine imbalance. I think if the cervix is removed there is no danger of carcinoma of the cervix developing and that you will prevent leucorrhœa.

THE ISOMETRIC METHOD OF X-RAY PELVIMETRY AS A ROUTINE PROCEDURE*

CHARLES M. MCLANE, M.D., NEW YORK, N. Y.

(From the Department of Obstetrics and Gynecology, Cornell University Medical College and the New York Hospital)

IN APRIL, 1942, Drs. Steele and Javert,¹ and in November, 1943, Javert² described the isometric technique of x-ray pelvimetry in conjunction with the Caldwell and Moloy stereoscopic method. The history of the development of the procedure, as well as a complete bibliography of x-ray pelvimetry in general, can be found in these papers and will not be included in this presentation. In both articles the authors suggest that the isometric method could be used alone but nothing further has been done to present this to the obstetric public. The combined methods have been used at the New York Lying-In Hospital for four years, and it is my feeling that the isometric technique is of great value and gives as much information about the pelvis and cephalopelvic relationship as any procedure yet described. It has the following advantages: (1) Only two x-ray pictures are necessary. (2) These can be taken with any modern x-ray machine in any hospital. (3) The measurements and classification can be done readily. (4) The interpretations and recommendations can be made after one acquires experience in the method but should probably be made by an obstetrician.

We do not at the moment advocate nor do we take x-rays routinely on all obstetric patients. X-rays are taken at or near term or during labor in the following groups of patients: (1) elderly primigravidas (35 years of age or over); (2) all primigravidas with breech presentations; (3) all patients whose pelvis are contracted by clinical measurements; (4) patients with history of dystocia, difficult labor or deliveries in previous pregnancies; (5) all patients in labor not previously x-rayed who are not making definite progress. At the Lying-In Hospital, we take on the average of thirty x-rays a month and deliver about two hundred fifty patients during the same period, pelvic series being done on 7.6 per cent of our clinic patients and 20.3 per cent of our private patients.

The isometric method, as we understand it and use it, is really a combination of the quantitative and qualitative aspects of x-ray pelvimetry. For the measurements we use the isometric method in its purest sense, and for the qualitative approach we follow the procedure of Caldwell and Moloy's morphologic classification and architectural studies, using, however, only a single anteroposterior film and a lateral one. We believe that, except for cephalometry on

*Read before a meeting of the New York Obstetrical Society on March 12, 1945.

the unengaged head, the isometric method, as described above, yields as much information as the stereoscopic method. In addition, we feel that the measurements of the transverse diameters of the pelvis, that is, the transverse of inlet, interspinous (ischial), and transverse of outlet, are more accurate when the isometric method is used. The method depends on the use of the distorted centimeter scale as shown in Fig. 1.

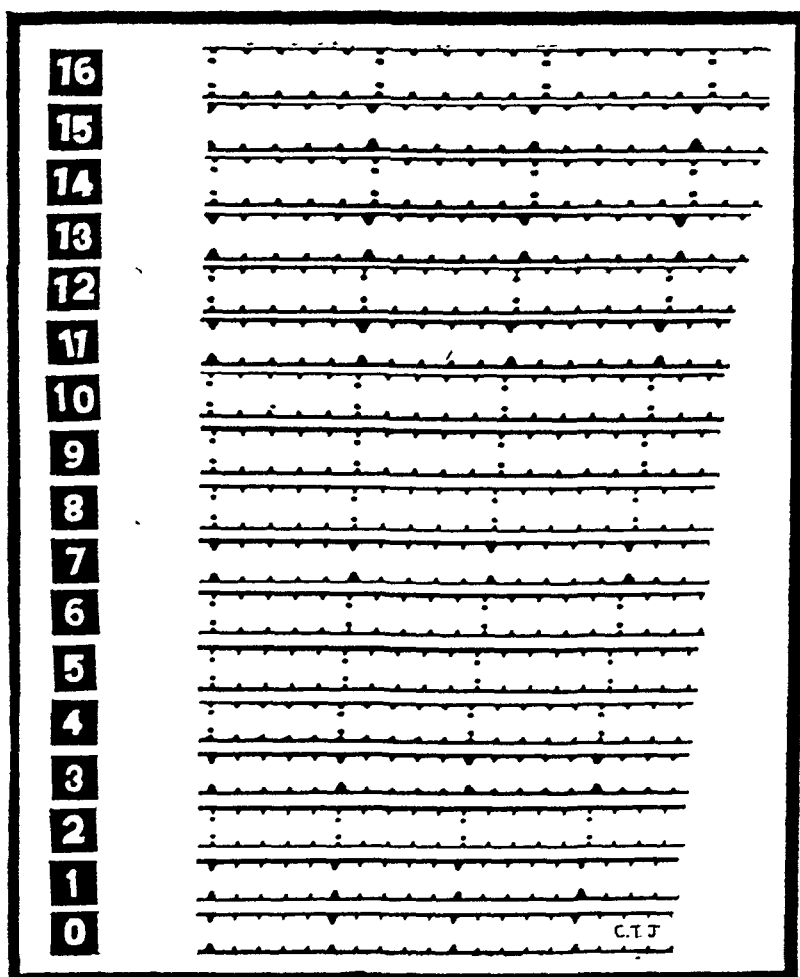


Fig. 1.—Distorted centimeter scale.

This scale is merely a series of pictures of a centimeter ruler taken at various distances from the x-ray table, the tube distance being 25 inches. The picture of the scale marked 0 was taken with the ruler lying on the x-ray table, and in subsequent pictures the numbers on the side represent the height in centimeters of the ruler above the x-ray table. Other factors being equal, the distortion of the scale naturally is altered by the distance of the x-ray film from the top of the x-ray table. In the machine we use, this distance is 4.5 centimeters. The scales can be made very simply for any x-ray table.

Technique

The technique of taking the two pictures has been described in great detail in the papers of Steele and Javert¹ and Javert² referred to above. Our only change has been to put three instead of two pillows under the patient's back to bring the pelvic inlet almost at right angles to the x-ray, thus giving us a less distorted view of the inlet. To summarize the technique briefly (Fig. 2): In the anteroposterior view the patient lies on the table with the shoulders resting on three pillows placed lengthwise and with a rolled sheet 4 inches thick placed under the lumbosacral curvature. The x-ray tube is centered over the patient on a line between the anterior superior spines and 25 inches from the x-ray film. A Bucky diaphragm is used, and one picture taken.

For the lateral picture (Fig. 3) the patient lies in the same position but is moved to a wooden table which is about the height of an ordinary stretcher. A notched metal centimeter scale is placed in front of the symphysis pubis in a vertical position. The x-ray table is turned vertically and the patient on the wooden table is placed in front of it with one hip touching the table. The x-ray tube is centered on a line drawn between the trochanters and the posterior superior spines and situated 36 inches from the film.

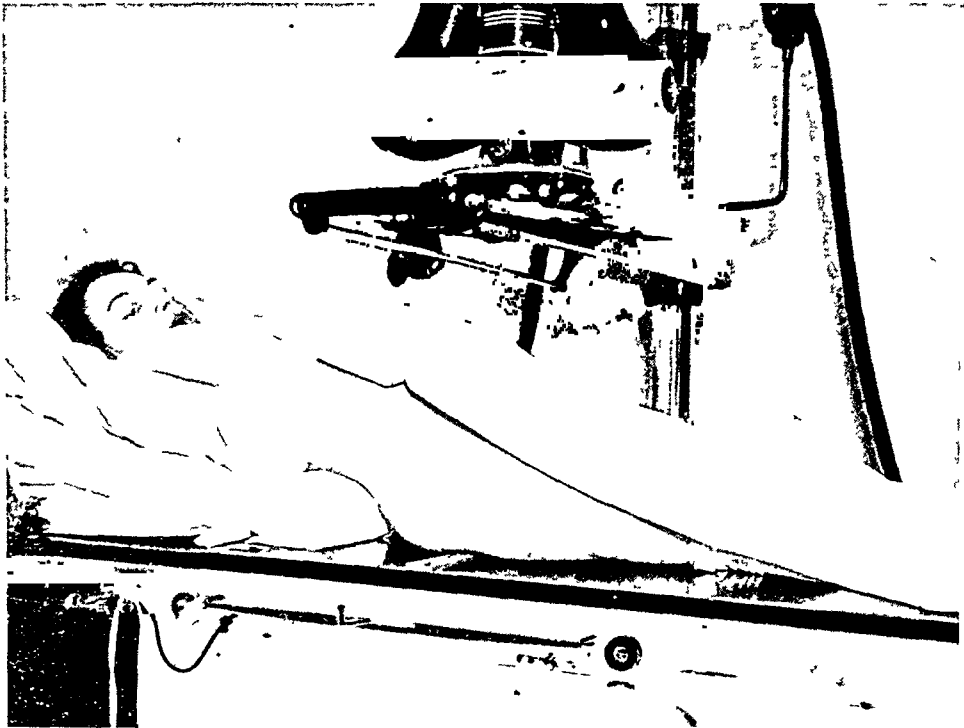


Fig. 2.—Technique of taking anteroposterior view of pelvis.

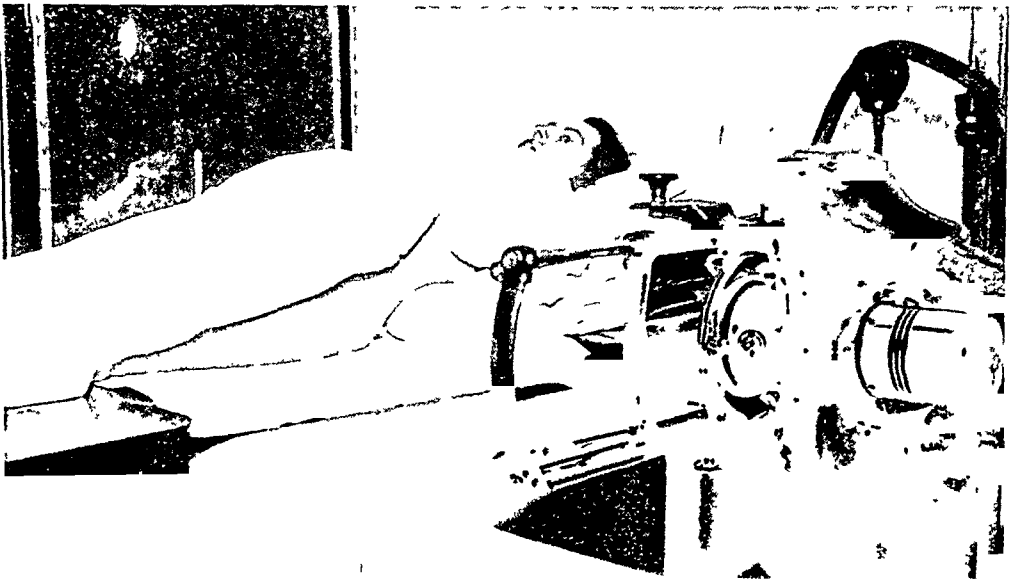


Fig. 3.—Technique of taking lateral view of pelvis.

The two developed x-rays are placed in a view box and the lateral film is studied first. (Fig. 4.) The following points are marked: The upper inner and lower border of the symphysis; the point at which the iliopectineal line crosses the sacrum, the inner tip of the fifth sacral vertebrae; the ischial spines; and the mid-point on a line joining the ischial tuberosities. A line is drawn connecting the upper and inner border of the symphysis and the point where the iliopectineal lines cross the sacrum; this line represents the obstetric conjugate. A second line is drawn at right angles to the obstetric conjugate passing through the base of the ischial spines. This divides the pelvis into an anterior and posterior seg-

ment. A base line is drawn across the film, representing the top of the x-ray table on which the metal rule rested.

The following measurements are made: The obstetric conjugate; posterior and anterior sagittal of inlet; posterior sagittal of midpelvis and outlet and anteroposterior diameter of outlet. Three heights are recorded: TR which represents the distance of the transverse diameter of the inlet from the base line of x-ray table, SP which is the height of the ischial spines from the table, and TI the height of the line joining the tuberosities of the ischium from the base line.



Fig. 4.—Anteroposterior and lateral views of pelvis.



Fig. 5—Measurement of head.

The lateral plate also yields the following information: The width of the apex and base of the sacro-sciatic notch, the inclination of the sacrum when compared with the inclination of the symphysis; the number of sacral vertebrae; the curvature of the first three sacral vertebrae; the curvature of the tip; the position of the coccyx; the lateral bore of the pelvis, that is, the relationship between a line drawn along the inner border of the symphysis and along the

first three sacral vertebrae, where these lines converge, diverge, or are parallel. We can also determine the station of the head and get a good idea of cephalopelvic relationship. If the head is engaged in the transverse, the biparietal diameter can be measured. (Fig. 5.)

In the anteroposterior film the following points are marked and connected by a line: The greatest transverse diameter of inlet, the ischial spines, and the points for measuring the tuberosities of the ischium. These latter points were described by Steele and Javert. Calipers are placed on the two points marking the transverse diameter of the inlet and then placed on the scale in the distorted centimeter scale that corresponds to the height TR in the lateral film. In a similar manner the interspinous and intertuberosus measurements are made, using the scale that corresponds to their heights as determined from the lateral film.

We have been using the single anteroposterior view for classifying the inlet according to the Caldwell and Moloy morphologic classification. Since we still use the combined isometric and stereoscopic method at the Lying-In Hospital, we have been able to compare our classification from the flat plate with that made in the stereoscope. In the last 100 cases the two have agreed 88 times; of the remaining 12 cases, the anterior segments have been classified differently in five cases and the posterior in six. In only one case have both segments been classified differently.

Using both plates, if necessary, the position of the head is determined, the prominence and shape of the ischial spines recorded, and the slope of the side walls estimated from the shape and position of the ischial spines and their relationship to the tip of the sacrum. The cephalopelvic relationship is estimated and a prognosis given on the basis of all of the above findings.

All the above information, as well as the stereoscopic measurements and two other diameters whose significance we are not prepared to discuss at present, is recorded on a special form. A copy of this report is placed in the x-ray folder, one sent to the referring doctor and one placed in the patient's chart. This affords the clinician a ready method of summarizing the findings and has proved an aid in deciding the correct disposition of the case.

To chart and summarize our results is somewhat of a problem, as many factors besides the cephalopelvic relationship enter into and alter the course of a given labor. During the past three years we have taken x-rays routinely in the five groups of patients previously described, yet during this time there has been a decrease in the number of sections done for disproportion and a decrease in the gross fetal mortality when compared to the previous three years. (Table I.) I quote these figures merely to show that x-ray pelvimetry does not increase the gross fetal mortality. By the latter term we mean deadborn, stillborn and neonatal deaths up to fourteen days postpartum.

TABLE I

Gross Section Incidence	1939 to 1941 incl.	2.6%
Gross Section Incidence	1942 to 1944 incl.	3.4%
Sections Done for Disproportion	1939 to 1941 incl.	36.7% of all sections
Sections Done for Disproportion	1942 to 1944 incl.	28.4% of all sections
Gross Fetal Mortality	1939 to 1941 incl.	3.56%
Gross Fetal Mortality	1942 to 1944 incl.	2.63%

To compare one method of x-ray pelvimetry with another is difficult but I feel that the isometric technique offers a little more than any of the now widely used techniques. Two less x-ray films are used than in the Caldwell and Moloy method and the expensive precision stereoscope is not required. The information obtained, with the exceptions stated previously, is just as comprehensive. It is far more accurate than the Ball technique, particularly in borderline cases. In our hands the measurements seem more exact than in the Thoms method and we feel that the Caldwell-Moloy classification of the pelvis is a more workable one than the latter. We do not feel as Thoms does that all pelvises can be put into only four groups based entirely on the relationship between the obstetric conjugate and transverse diameter of inlet. When the size of the fetal head approaches that of the pelvic inlet, the shape of the inlet is of paramount importance and the actual measurements are definitely secondary. We have had no experience with the Johnson-Hodges technique but cannot see any advantages it has over the isometric method.

Conclusions

The isometric method of x-ray pelvimetry has been presented as an accurate, comprehensive, and relatively inexpensive way of measuring the female pelvis and of studying all its morphologic characteristics. It can be done without complicated equipment, mathematical formulas, or prolonged technical training. More information can be obtained than by clinical examination, and in the small percentage of borderline cases definite help can be given to the clinician in his treatment of a patient. It is my feeling that, in the practice of obstetrics in the future, some accurate method of x-ray pelvimetry will be as much a part of the routine examination as an x-ray of the chest is now, in the care of a patient with tuberculosis.

I wish to thank Mrs. Mildred Powlitis Hartman for her invaluable aid in the preparation of this paper.

References

1. Steele, K. B., and Javert, C. T.: *AM. J. OBST. & GYNEC.* 43: 600, 1942.
2. Javert, C. T.: *North Carolina M. J.* 4: 1, 1943.

33 EAST 68TH STREET

Discussion

DR. ANTHONY D'ESOPO.—The various methods in use for studying the pelvis by the x-ray can be divided into two classes, the qualitative and quantitative methods. A good example of the quantitative is the one proposed by Ball in which the smallest pelvic diameter is measured and to this is related the volume of the fetal head; from a formula that he has worked out you determine whether the head will pass through the pelvis or not, without consideration of the pelvic architecture or any of the many variable relationships that may pertain as the head passes through the pelvis. The method we like at the Sloane Hospital is perhaps the other extreme, a method that relies primarily on qualitative values without much consideration of numerically expressed diameters as such.

Now it does not necessarily follow that one or the other method will finally be the one that we will all agree upon or the one that will come into general use. It may well be that a combination of these two methods will prove to have the greatest advantages and I believe that the method presented here attempts to include both these aspects of x-ray pelvimetry. Personally, I feel somewhat lost when I try to evaluate the pelvis in terms of diameters. The stereoscopic view of the relationship between the head and the pelvis gives a three-dimensional concept which permits complete structural visualization that greatly augments the information that we obtain by digital examination.

DR. HARRY ARANOW.—I have used the Weitzner method at Morrisania Hospital and the Snow method at the Bronx Hospital and have come to the conclusion that the final test is the judgment of the obstetrician.

I am never entirely satisfied with either of these methods. The Snow method has an occasional mistake here and there, and so has the Weitzner. All the methods have many possibilities of error because the results depend on the angle and the distance from the x-ray tube.

The main thing is the impression that you get from looking at the picture and then checking on it with your own clinical sense. I think the simpler the method, the more useful it is for the average obstetrician.

DR. HOWARD C. MOLOY.—Dr. McLane has made certain technical suggestions which have considerable significance.

I should first call attention to the fact that in Dr. Stander's clinic in the last three years, there has been a definite reduction in the fetal mortality rate without an increase in the incidence of cesarean section. To be sure, roentgen pelvimetry cannot take full credit for this favorable result, because there has been a general reduction in mortality rates throughout the country. Nevertheless, in many instances, the information contributed by roentgenologic examination has been a factor in saving fetal life. That is quite a far cry from the criticisms offered in earlier years, that roentgenologic methods of examination would result in a loss of skill in the use of our hands in obstetric maneuvers. I believe, on the

contrary, an understanding of the varied mechanisms of labor and careful appreciation of the size of the pelvis and its shape has enabled us to perform correct maneuvers without the trial and error that frequently resulted in obstetric difficulty in the past. Therefore, we have no apologies to make in regard to the beneficial results which can be obtained from a correct interpretation of the roentgen films when we use and understand the principles of the technical methods employed for the examination.

There are probably eight or ten methods, more or less, which have been devised throughout the country, which have been carefully described and, in the hands of their originators and others, are giving accurate results.

I feel all clinics which make extensive use of roentgen pelvimetry have had occasion to conduct an examination upon patients who have been studied by a different technique. In most instances the two techniques agree, but occasionally great discrepancies are found. Personally, I know of several cases in which the measurement of the interspinous diameter varied considerably and inaccurate findings caused concern until further x-rays showed the pelvis to be ample. Such errors are due to failure to carry out the technique as described by the originator of the method, because *measurements vary according to the accuracy of the technique employed*, and there must be cooperation on the part of the roentgenologist and obstetrician in regard to the carrying out of the written procedure.

There are a number of things that interested me in connection with this method.

First, the use of the pillows is a very important addition; by elevating the shoulders and increasing the size of the lumbosacral pad it is possible to obtain a good inlet view in which shape is portrayed accurately. In the semisitting position the long axis of the uterus at term assumes a position along the line of the central ray, and it requires a strong dosage to penetrate the long axis of the child. While this gives a very good inlet view, the outline of the inlet is somewhat difficult to see and the position fails to give complete silhouette of the fetus, which is important in visualizing the attitude of the baby. In the anteroposterior (view), as described by Dr. McLane, we see the fetal attitude because we have a good profile view of the baby.

Since the concentration of the dosage used varies according to the square of the distance, it naturally follows that the breech of the child, with the mother in the semisitting position, receives an intensive dosage. While no harm has been shown to occur, nevertheless I think it would be advisable to avoid such a possibility.

The other matter of interest is the lateral view. The skeletal pelvis in the lateral view can be shown to advantage whether the patient is erect or supine. In so far as I can determine, it is generally accepted that the standing lateral has many advantages over the supine lateral; not only does it portray the outline of the birth canal from the lateral viewpoint, but it aids in allowing gravity to force the head to the lowest level. In other words, in cases of placenta previa and in disproportion, the head is held high and cannot engage. It would be of interest if this technique could be worked out to apply to the standing lateral.

DR. MC LANE (Closing).—I agree entirely with Dr. D'Esopo that a combination of the two extremes is what we will eventually adopt. I don't think this method is that ideal combination, but I believe that if we try to combine the quantitative with the qualitative, those who are interested in this combination will get together, bury the hatchet, and arrive at a final solution of the problem.

In reply to Dr. Cosgrove: In my opinion, the clinical measurements we make in an effort to determine the obstetric conjugate or true conjugate, are most inaccurate. A good many years ago when we first became interested in this subject, Dr. Steele, Dr. Wing, and I checked the true conjugate measurements against the diagonal conjugate measurements and found no correlation whatsoever. Clinically we used to subtract 2 or $2\frac{1}{2}$ cm. and in difficult cases subtracted 3 cm., why, I don't know, because there is no connection at all. We found in 200 cases that if you took $2\frac{1}{2}$ or 3 cm. as the measurement to be subtracted from the diagonal conjugate to find the true conjugate, there was a very small group. The whole group varied anywhere from the diagonal conjugate being more than 3 cm. greater than the true conjugate to its actually being less than the true conjugate. I do not think that clinical measurements of the pelvic inlet are worth anything at all.

Dr. Heaton was bitter in his criticism. I mentioned Caldwell and Moloy about every fifteen lines. I didn't want you to think that I was uncovering anything new. I was giving them credit as often as I could without their writing the paper. We have tried very sincerely to sell the stereoscopic method to the men who come to visit our clinic. I have talked to them

and have had them look into the stereoscope but they couldn't see anything that was understandable to them. I could not train them to use it and so I came to the conclusion, as far as I was concerned, that it was a hopeless proposition.

I believe the qualitative method of Caldwell and Moloy is the best method we have for studying cephalopelvic disproportion, but you cannot sell it to the public. You must give measurements, you cannot sell an obstetrician relationships, you must have figures—that is true and Dr. Moloy, I hope, will back me up. That is why we emphasize the measurements. If you teach a man measurements, that is something he can use.

The Weitzner rule was described in 1932 or 1934 in the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY. He strapped a ruler to the back at the level of the sacrum and took a picture in the erect posture. We use a metal rule and put it between the patient's legs.

I am not entirely prepared to combat Dr. Moloy's criticism of the standing lateral. We took standing laterals for a good many years and I was unimpressed by any heads jumping in the pelvis that were out of the pelvis when the patient was lying down. I also think that if any patient in whom you are interested has cephalopelvic disproportion, there is going to be very little descent of the head, irrespective of its position, before going into labor.

Dr. Moloy told me that he was going to question the lying down lateral position. I feel you should take both pictures with the patient in the same position, whether lying down or standing up, but not take one lying down and one standing up and transpose from one to the other. I feel that in our lateral picture if the head is at or near the pelvic brim, you can get a fairly good estimate of whether or not the head is going to go through. We are very cautious in our prognostications because too many factors enter into the course of labor besides the size of the head and the size of the pelvis.

ANDROGEN THERAPY OF MENOPAUSAL SYMPTOMS IN CANCER PATIENTS*

S. B. GUSBERG, M.D., NEW YORK, N. Y.

(From the Sloane Hospital for Women and the Department of Obstetrics and Gynecology,
Columbia University)

Introduction

TREATMENT of the menopausal patient with estrogenic substances is a well-established and effective method of controlling the uncomfortable symptoms which sometimes occur with the decline and cessation of ovarian activity. The explanation for the effectiveness of this therapy has been studied for many years; some observers suggest that this efficiency in relation to the vasomotor symptoms of the menopause is probably due to inhibition of overactivity of the anterior pituitary gland. This explanation would be in accord with the well-known reciprocal interaction of the pituitary gland and the various glands of internal secretion which it governs.

We have been dissatisfied with the use of stilbestrol in a certain group of menopausal patients in whom we believed the stimulating effect of estrogen was contraindicated. This includes those who have been treated for some form of cancer of the reproductive organs and also some of those in whom estrogenic therapy has provoked uterine bleeding. It is not within the province of this presentation to discuss the possible relationship between estrogens and carcinogenesis. This relationship has been studied and debated by numerous careful observers for many years; our own data and conclusions will be presented elsewhere. Suffice it to say that in the human species whose genetic

*Presented at the New York Academy of Medicine, Section of Obstetrics and Gynecology, Jan. 23, 1945.

pattern is so complex, we think it unwise to subject susceptible tissue to a stimulating substance; those individuals who have already demonstrated the responsiveness of one of the reproductive organs to whatever abnormal stimulus develops carcinoma would seem especially unfavorable subjects in whom to administer a cell-proliferating substance like estrogen. We have also become impressed with the fundamental error in continuing estrogenic therapy in any postmenopausal individual for long periods of time for it creates a habit which is difficult to break; we have sought a method to remedy this condition.

These considerations, together with the occasional production of abnormal endometrial patterns in patients who have developed stilbestrol bleeding led us to the use of androgen therapy for this selected group of menopausal patients.

In animals, a variety of uterine and vaginal responses have been produced by androgens (Salmon, Geist, et al.¹), some of a stimulating nature, others of an inhibitory nature. There is a suggestion in some of this work that mature animals most commonly show an inhibitory response, especially with small doses. Inhibition of reproductive tract activity in animals by androgens has been demonstrated by many workers, among them Ilrke and D'Amour,² Robson,³ Zuckerman,⁴ and Hartman.⁵ Inhibitory action on menstruation has also been demonstrated in humans by Papanicolaou, Ripley, and Shorr,⁶ Loeser,⁷ Geist, Salmon, and their associates,¹ Huffman,⁸ Greenblatt,⁹ and others. In the increasing literature concerning the use of androgens for abnormal uterine bleeding, it would appear that doses of testosterone propionate under 400 to 500 mg. monthly will reduce bleeding effectively without changing the endometrial pattern, while doses higher than this are required to produce endometrial regression. There are no reports of stimulation of the human endometrium by androgens.

Engle and Smith¹⁰ working with castrated mature Rhesus monkeys were able to maintain endometria primed by the use of estrogens and progesterone, with short courses of testosterone propionate treatment. They suggest, however, that this sequence of administration may not inhibit the pituitary as androgens are believed to do when given throughout the menstrual cycle. It has been suggested by other workers (Salmon, Geist, et al.,¹ Huffman,⁸ Greenhill and Freed,¹¹ and Aub²⁸) that inhibition of the pituitary is the probable mode of action of androgen therapy in the control of uterine bleeding. In menopausal patients there has been more direct evidence that androgen therapy can reduce anterior pituitary hyperactivity. Nathanson and Towne¹² and Salmon¹³ clearly demonstrated reduction in urinary gonadotropins as treatment proceeded and symptoms were ameliorated. Similar findings were obtained by Shorr, Papanicolaou, and Stimmel,¹⁴ Laroche, et al.,¹⁵ and Rothermich and Foltz.¹⁶

The use of androgen therapy for the menopausal syndrome has been suggested by several workers since 1936. In that year Mocquot and Moricard,¹⁷ and Margeil and Zwilling¹⁸ reported the effectiveness of this therapy. Since that time there have been several small groups of cases reported, including those of Kurzrok, Birnberg and Livingston,¹⁹ Mandy and Mandy,²⁰ McCullagh and McGurl,²¹ Geist and Salmon,²² Kurzrok and Rothbart,²³ Silberman, Radman, and Abarbanel,²⁴ Greenhill,²⁵ Joel,²⁶ Loeser,²⁷ and Greenblatt.⁹ For the most part these investigators used testosterone propionate parenterally, though several mention the use of methyl testosterone by mouth; in some instances a combined stilbestrol-androgen therapy was given. In general the results of treatment were excellent. In none of these reports is there any evidence of uterine stimulation by this androgen therapy.

The fear of untoward symptoms and masculinization has deterred many gynecologists from the use of androgen therapy. This healthy regard for the patient's complete safety is readily understandable when one studies the undesirable effects produced by large or prolonged dosage. Our interest in the possible use of this type of endocrine preparation led us to a series of preliminary observations which convinced us of the safety of this technique in the relatively small dosage required for the treatment of the menopausal syndrome. We therefore proceeded to its use in selected patients.

TABLE I. ANDROGEN TREATMENT OF MENOPAUSAL SYMPTOMS

NAME NO.	AGE (YR.)	DESCRIPTION OF MENOPAUSE	PRINCIPAL SYMPTOMS	PREVIOUS TREATMENT	PRESENT TREATMENT	RESULT	SIDE EFFECTS
E. R. 520851	61	Radium and hysterectomy 2 years ago for corpus carcinoma	Hot flashes	Androgen, small amount	Methyl testosterone 10-20 mg. O.D. 2 x 1 mo. courses	Improved markedly. Not permanent. Appetite and weight increased	0
D. W. 502742	24	Radium and hysterectomy for corpus carcinoma 1 year ago	Flashes, fatigue, loss of appetite	Stilbestrol	Testosterone propionate, 75 mg. per week for 1 month. Methyl testosterone, 10 mg. daily for 6 weeks	Excellent. Flashes gone. Weight, strength, appetite markedly improved. Slight return of symptoms. More effective relief than stilbestrol	Slight hirsutism of lip and chin. Slight engorgement of clitoris. No change in libido. Occasional leg cramps
M. Q. 58036	50	Radium for fibroids, recent	Flashes. Nervousness	Stilbestrol	Methyl testosterone 10 mg. daily for 4 weeks	Excellent. Flashes, nervousness, strength all improved. No return. More effective than stilbestrol	0
T. H. 699551	51	Hysterectomy and radiation 1 year ago for primary carcinoma of tube	Flashes	None	Methyl testosterone 10 mg. daily for 4 weeks	Excellent. Flashes gone, no return	0
P. M. 710670	31	Radiation. Carcinoma of cervix, recent	Flashes	None	Methyl testosterone 10 mg. daily for 8 weeks	Excellent. Flashes gone. Very slight return when off medication	0
F. F. 713316	29	Radiation. Carcinoma of cervix, recent	Flashes	None	Methyl testosterone 20 mg. daily for 6 weeks; 10 mg. daily for 2 weeks	Excellent. Flashes gone. Appetite, strength, weight improved. Slight return when off medication	General stimulation
S. Q. 675012	45	Hysterectomy and oophorectomy for corpus carcinoma—recently P.O.	Flashes, sweats, weakness	None	Testosterone propionate, 75 mg. Methyl testosterone, 20 mg. daily for 2 weeks	Improved, immediately P.O. Difficult to evaluate. Never any further symptoms	0
H. V. 549137	26	Oophorectomy 5 years ago	Flashes, fatigue	Much stilbestrol. Relief not permanent. G.I. symptoms	Testosterone propionate, 150 mg. Methyl testosterone, 20 mg. daily for 2 weeks, 10 mg. daily for 2 weeks.	Marked improvement. Strength and flashes. Not permanent, slight return. More effective than stilbestrol	Slight breast pain. Questionable slight hirsuties
C. T. 658198	47	Radiation for dysfunctional bleeding 3 years ago	Flashes, nervousness	Stilbestrol. No permanent relief. G.I. symptoms	Testosterone propionate, 150 mg. Methyl testosterone, 20 mg. daily for 2 weeks, 10 mg. daily for 4 weeks	Excellent result to flashes and nervousness. No return of symptoms. Much more effective than stilbestrol	0
D. P. 683690	40	Radiation for carcinoma of cervix, recent	Flashes	0	Methyl testosterone, 20 mg. daily for 4 weeks	Excellent result on 20 mg. O.D. Slight return with less	General stimulation
G. K. 667553	49	Radiation for dysfunctional bleeding 1 year ago	Flashes, nervousness, dizziness	Stilbestrol. No permanent relief	Methyl testosterone, 20 mg. daily for 4 weeks, 10 mg. daily for 2 weeks	Excellent result. Symptoms relieved. No return. More effective than stilbestrol	General stimulation
M. G. 738198	50	Spontaneous, several years ago	Flashes, nervousness	Much stilbestrol. Bleeding	Testosterone propionate, 150 mg. Methyl testosterone, 20 mg. O.D. for two weeks	Good result. About as good as stilbestrol. Stopped bleeding. Result not permanent	0

C. R.	54	Spontaneous, recent	Flashes, dizziness, headaches	0	Methyl testosterone, 20 mg. daily for 2 weeks, 10 mg. daily for 2 weeks	20 mg. 10 mg.	Excellent	General stimulation
465049								
P. S.	47	Oophorectomy with hysterectomy, recent	Flashes	0	Methyl testosterone, 20 mg. daily for 4 weeks	20 mg. 10 mg.	Excellent	0
639300								
D. F.	34	Oophorectomy 6 months ago	Flashes	0	Methyl testosterone, 20 mg. daily for 2 weeks, 10 mg. daily for 2 weeks	20 mg. 10 mg.	Excellent. Slight return	0
563292								
E. G.	48	Radiation for carcinoma of cervix 1 year ago	Flashes, headaches, poor appetite	0	Methyl testosterone, 20 mg. daily for 2 weeks	20 mg.	Excellent. All symptoms relieved	General stimulation
708360								
E. P.	46	Radium menopause. Fibroids 8 months ago	Flashes	0	Methyl testosterone, 20 mg. daily for 4 weeks	20 mg.	Excellent	0
700065								
M. B.	46	Spontaneous menopause. Fibroids	Flashes, nervousness	0	Methyl testosterone, 20 mg. daily for 4 weeks	20 mg.	Excellent. All symptoms relieved. Mild return	0
321196								
E. W.	52	Radiation for carcinoma of cervix 4 years ago	Flashes, fatigue, nervousness	Stilbestrol	Methyl testosterone, 20 mg. daily for 6 weeks	20 mg. 10 mg.	Good. Nervousness and flashes improved. Fatigue somewhat better. Slightly more effective than stilbestrol; probably more permanent	Libido increased due to local receptivity. Occasional leg cramps
712508								
Mrs. T.	41	Radiation for (?) carcinoma of cervix 7 years ago	Flashes, nervousness, fatigue, depression	Stilbestrol	Methyl testosterone, 20 mg. daily for 6 weeks	20 mg.	Questionable benefit. Possible slight improvement. Trial inadequate	0
H. M.	48	Spontaneous menopause 5 years ago	Flashes, nervousness, fatigue	Much stilbestrol. Bleeding	Methyl testosterone, 20 mg. daily for 4 weeks, 10 mg. daily for 2 weeks	20 mg. 10 mg.	Excellent result. All symptoms relieved. Very slight return. More effective and more permanent than stilbestrol	General stimulation. Appetite and weight increase
R. G.	53	Spontaneous menopause, recent	Flashes, nervousness	Stilbestrol caused spotting	Methyl testosterone, 20 mg. daily for 2 weeks	20 mg.	Excellent. More effective than stilbestrol	General stimulation
334513								
K. H.	28	Radiation for carcinoma of cervix 2 years ago	Flashes, nervousness	Much stilbestrol. G.I. symptoms	Methyl testosterone, 20 mg. daily for 4 weeks	20 mg.	Improved. Moderate return	0
680757								
M. S.	46	Oophorectomy, hysterectomy for carcinoma of ovary, recent	Flashes, nervousness, fatigue	Stilbestrol. G.I. symptoms	Methyl testosterone, 20 mg. daily for 4 weeks	20 mg.	Excellent result. All symptoms relieved. More effective than stilbestrol	General stimulation. Marked increase in weight, appetite, and strength

O. D. = Daily.

P. O. = Postoperative.

G. I. = Gastrointestinal.

Methods and Data

We have confined our study for the most part to a selected group of patients who have been subjected to surgery, radiation, or both, for neoplastic disease or dysfunctional bleeding from the reproductive tract. Our group is composed of 24 patients treated for menopausal symptoms by androgens. This number is small, but we believe the uniformity of the results enhance their significance. It is our opinion that the percentage of menopausal women who require endocrine treatment is small; the majority of patients undergoing either a spontaneous or an artificial menopause require no treatment. A small additional group which is symptomatic can be relieved with small doses of sedative.²⁹ In addition, the effectiveness and safety of stilbestrol for many patients who do require endocrine treatment leaves a small group for whom other therapy may be indicated. Unfortunately, our controls are incomplete, but half our patients had received previous stilbestrol treatment.

TABLE II. SUMMARY OF RESULTS

24 Cases					
Symptomatic menopausal patients	23 Cases				
	Benefited from androgen therapy	16 Cases			
		Early menopausal patients.			
		Uniformly excellent result			
			6 Cases		
			Late menopausal patients		
			Improved	2 Cases	
				Possible slight hirsutism. Oral and parenteral therapy	1 Case
					Late unimproved. Large psychoneurotic element

We have used methyl testosterone* for the most part, though an occasional patient was given testosterone propionate early in the study. The course of therapy which we found most effective extended over approximately six to eight weeks: 20 mg. of methyl testosterone by mouth daily for four weeks, then 10 mg. daily for two weeks thereafter. This therapy was usually enough to control symptoms. We usually allow several intervals of one week without treatment during the course. Our results are tabulated in Tables I, II, and III.

*Methyl testosterone (Metandren) and testosterone propionate (Perandren) were supplied to Dr. E. T. Engle by the Ciba Company, through the courtesy of Mr. R. H. Mautner.

Discussion of Results

Androgen therapy has strikingly benefited the vasomotor symptoms of the menopause in 23 of our 24 cases. For those patients whose menopause was recent, in whom one might reasonably postulate a significant endocrine imbalance, results were excellent and uniform. For late cases in whom one might postulate a greater functional than chemical imbalance, results were less striking, though we observed some benefit in all patients who received an adequate course of treatment.

TABLE III. COMPARISON: STILBESTROL AND ANDROGEN THERAPY

12 Cases Previous treatment with stilbestrol	10 Cases			
	Greater benefit from androgens	7 Cases Untoward effects from stilbestrol. Vaginal bleeding or gastrointestinal symptoms		
			2 Cases Possible slight hirsutism. Oral and parenteral therapy	2 Cases Large psycho-neurotic element

Of 12 patients who had had previous stilbestrol therapy, ten were benefited to a greater degree by the androgens. The other two had taken stilbestrol for years and the habit was difficult to break. We found it possible in some instances to achieve this withdrawal from all endocrine therapy by a course of androgen treatment, but in others the functional orientation of the patient to her bottle of stilbestrol tablets had come to play too protective a role in her psychic well-being. We have no explanation for the apparent greater permanence of the result with androgen therapy. It may have some relation to our plan of management which never sought to completely obliterate vasomotor symptoms but simply to reduce them to the point of tolerance. This may allow more natural endocrine readjustment. Frequently also, it will be noted that symptoms recurred to a minor degree when therapy was stopped. This rarely called for renewal of therapy, for the recurring symptoms were usually of a degree which produced little discomfort. However, our follow-up is not long enough as yet to evaluate this permanence completely.

We have noted that with male sex hormone therapy many patients experience a feeling of stimulation and general well-being. There was frequently marked loss of nervousness, increase in appetite, weight, and strength, and at times a marked sense of exhilaration. These effects have also been noted by other observers of androgen-treated patients. They may be partially dependent on the well-known nitrogen-sparing action of androgens.

We have not seen untoward reactions of any significant degree in this group of patients. This is in accord with published data which place the limit of safety in relation to masculinizing symptoms considerably above the amount we have found it necessary to use. We have encountered slight increase in lip hirsuties in two of our cases, both of whom were given testosterone propionate in addition to methyl testosterone. We have also noted slight increase in the size of the clitoris in one of these cases. Another patient who had been given

methyl testosterone alone volunteered the information that she had noted a sense of engorgement about the clitoris and some increase in libido. Two patients in our group also noted occasional mild leg cramps during the course of therapy, but these were never striking enough or persistent enough for us to be certain they were definitely associated with the androgen administration.

If the vasomotor symptoms of the menopause are presumed to be due to increased anterior pituitary activity following decline in ovarian activity, it is to be expected that either estrogen or androgen therapy will diminish it and so control these symptoms.

We have encountered no instance of androgen-induced uterine bleeding in our series.

Summary and Conclusions

1. The rationale and literature of androgen therapy of the menopausal syndrome are discussed.

2. A group of menopausal patients treated with methyl testosterone is presented. We have found this a safe and effective means of controlling menopausal symptoms. In a small group of patients who have had both medications, we have observed a somewhat greater benefit from androgens.

3. For the small number of menopausal women who require endocrine therapy we have urged the use of androgens rather than estrogens in the following groups:

- a. Patients who have been treated for cancer of the reproductive tract or breast.
- b. Patients who have been treated for abnormal uterine bleeding during the climacteric.
- c. Patients who have developed uterine bleeding while under treatment with estrogenic substances.
- d. Patients who require endocrine therapy for vasomotor symptoms before their menses have completely ceased.
- e. Patients who have become addicted to stilbestrol by long-continued usage.

The author wishes to acknowledge the advice and encouragement of Dr. B. P. Watson and Dr. W. E. Studdiford in this work. Also, to Dr. J. A. Corseaden and Dr. Earl T. Engle, the author wishes to express his indebtedness for their constant aid in the supervision and study of these patients.

References

1. Salmon, U. J., Geist, S. H., Gaines, J. A., and Walter, R. I.: *AM. J. OBST. & GYNEC.* 41: 990, 1941.
2. Ilrke, I. A., and D'Amour, F.: *Am. J. Physiol.* 96: 289, 1931.
3. Robson, J. M.: *Proc. Soc. Exper. Biol. & Med.* 35: 49, 1936.
4. Zuckerman, S.: *Lancet* 2: 676, 1937.
5. Hartman, C. G.: *Proc. Soc. Exper. Biol. & Med.* 37: 87, 1937.
6. Papanicolaou, G. N., Ripley, H. S., and Shorr, E.: *Endocrinology* 24: 339, 1939.
7. Loeser, A. A.: *Lancet* 1: 373, 1938.
8. Huffman, J. W.: *AM. J. OBST. & GYNEC.* 40: 675, 1940.
9. Greenblatt, R.: *J. A. M. A.* 121: 17, 1943.
10. Engle, E. T., and Smith, P. E.: *Endocrinology* 25: 1, 1939.
11. Greenhill, J. P., and Freed, S. C.: *AM. J. OBST. & GYNEC.* 39: 636, 1940.
12. Nathanson, I. T., and Towne, L. E.: *Endocrinology* 25: 754, 1939.
13. Salmon, U. J.: *Proc. Soc. Exper. Biol. & Med.* 37: 488, 1937.
14. Shorr, E., Papanicolaou, G. N., and Stimmel, B. F.: *Proc. Soc. Exper. Biol. & Med.* 38: 758, 1938.
15. Laroche, G., Simmonet, H., and Bompard, E.: *Compt. rend Soc. de biol.* 129: 953, 1938.
16. Greenhill, N. O., and Foltz, L. M.: *Endocrinology* 27: 37, 1940.
17. Mocquot, P., and Moricard, R.: *Bull. Soc. d'obst. et de gynéc.* 25: 787, 1936.
18. Margeil, E., and Zwilling, G.: *Polska gaz. lek.* 15: 815, 1936.
19. Kurzrok, L., Birnberg, C. H., and Livingston, S.: *Endocrinology* 24: 347, 1939.
20. Mandy, T. E., and Mandy, A. J.: *West J. Surg.* 48: 604, 1940.
21. McCullagh, E. P., and McGurl, F. J.: *J. Urol.* 42: 1265, 1939.
22. Geist, S. H., and Salmon, U. J.: *J. A. M. A.* 117: 2207, 1941.

23. Kurzrok, L., and Rothbart, H.: Am. J. Surg. 56: 636, 1942.
 24. Silberman, D., Radman, H. M., and Abarbanel, A. R.: AM. J. OBST. & GYNEC. 39: 332, 1940.
 25. Greenhill, J. P., ed.: Year Book of Obstetrics and Gynecology, 1943.
 26. Joel, C. A.: J. Clin. Endocrinol. 2: 116, 1942.
 27. Loeser, A. A.: Med. Press. 210: 240, 1943.
 28. Aub, J. C.: New England J. Med. 222: 877, 1940.
 29. Buxton, C. L.: J. Clin. Endocrinol. 4: 592, 1944.
-

LACTOBACILLUS THERAPY IN VAGINITIS DUE TO TRICHOMONAS

LEO BRADY, M.D., AND ROGER D. REID, PH.D., BALTIMORE, MD.

(From the Department of Gynecology of the Johns Hopkins Hospital and University)

IN 1941 the authors of this report read a paper¹ before the annual meeting of the Southern Surgical Association on the treatment of *Trichomonas vaginalis* vaginitis with the lactobacillus. That report was based on the study of 50 patients treated with tablets containing viable lactic acid forming bacilli. We now wish to present our results in a second series of cases treated in this manner.

In our first paper we stated that this method of treatment usually gave quick relief from symptoms, and in the great majority of instances, the vagina became free of trichomonas and remained so. At the time of our first report, we already had many patients who had been examined monthly for at least six months after treatment had been discontinued, and who remained free of trichomonads. There were, however, as we emphasized at that time, a few recurrences, or reinfestations, so, in spite of what we considered markedly good results in most cases, no claim was made that this method of treatment would completely eliminate recurrences or that it would even temporarily relieve the symptoms in every case.

The tablets used are prepared for us under the careful supervision of the bacteriologist, Dr. John H. Brewer. The strain of lactobacillus used in this work was obtained from the United States Department of Agriculture and is known as Hansen's strain of *Lactobacillus bulgaricus*. The actual preparation of the tablets is as follows:

Sterile skim milk is inoculated with the culture. After forty-eight hours' incubation, each 1,000 c.c. of this culture is mixed with 325 grams of XXXX sugar and milk sugar. This is thoroughly dissolved in the milk and the mixture is spread in thin layers on enamel pans and dried.

The mixture is scraped from the pans, broken into bits, and replaced in a drier to complete desiccation. When completely dried, 6 c.c. of white mineral oil and 38 Gm. of starch are added. The mixture is then pressed into tablets. Each one weighs 1.3 Gm., and represents 1.28 c.c. of original culture.

The idea of trying to free the vagina of trichomonads by implanting lactic acid-forming bacilli occurred to us after we had made a careful study of the normal defensive mechanism of the vagina which depends primarily on the three following conditions: First, that the vaginal secretion remains at its normal low pH; second, that the Döderlein or vaginal lactobacilli are present in sufficient numbers to form lactic acid; and finally, that there is sufficient carbohydrate, perhaps in the form of glycogen, in the vaginal epithelial cells or spaces between

them to afford adequate nourishment for the continued growth and activity of the Döderlein bacilli.

Some gynecologists, feeling that the most important part of this mechanism is that the vaginal secretion be kept in its normal low pH of about 5.5, have advised that in trichomonas infestations the only treatment should be the use of lactic acid or vinegar douches. Such treatments do give the patient considerable relief, but are not sufficient in themselves to correct the condition completely. Few, if any, cures have been brought about by simply using acid douches.

Other investigators, particularly Adair and Hesseltine,² have believed that in the treatment of *Trichomonas vaginalis* vaginitis the most important therapeutic measure is to furnish sufficient nourishment to maintain a normal bacterial flora and, hence, they recommended in 1936 that tablets containing 95 per cent lactose and 5 per cent citric acid be used. Karnaky⁴ with the same idea became enthusiastic over the use of vaginal suppositories containing lactose and dextrose. The preparation which he recommended, and which was placed on the market under the trade name of Floraquin, also contains an antiseptic known as Diodoquin, but the antiseptic is thought to have less therapeutic value than the sugars. Prior to our first publication, one of us (Brady) had used floraquin in a large number of cases, with some satisfactory results. However, there were in the series quite a few patients who continued to harbor the parasites in the vagina and to have recurrences of leucorrhea and pruritis with the menstrual periods. Being rather discouraged by the results obtained from the numerous preparations that had been recommended for the treatment of vaginitis due to the *Trichomonas vaginalis*, we decided, as we stated in our first publication, to attempt to build up the vaginal defense by simultaneously carrying out several measures. Not only was nourishment suitable for the growth of Döderlein's bacillus to be introduced into the vagina, but also viable lactobacilli.

Before lactobacillus tablets were available, we used lactobacilli in the following manner: Two lumps of ordinary sugar were coated with a thin film of the culture and then placed in the vagina. Quite naturally the heat of the tissues soon melted the sugar, converting it into a syrup which ran out of the vagina. Tampons made of ordinary cotton were of no help as they quickly absorbed the syrup and prevented its coming in contact with the vaginal epithelium. Tampons made of nonabsorbent cotton were then used, with more success. In fact, many women obtained prompt relief by this crude treatment.

Ever since starting this work, we have been interested in determining the number of live lactic acid-forming bacilli to the tablet. The method used in calculating this is the following: Ten tablets, selected at random from each lot, are dissolved in 100 c.c. of physiologic saline (0.85 per cent). Then 1 c.c. of this solution is transferred to a tube of saline containing 9 c.c., making a 1:100 dilution of the tablet. This is well mixed and 1 c.c. is added to 9 c.c. saline, making a 1:1,000 dilution. This process is repeated until all dilutions through 1:100,000 have been made. One cubic centimeter of each dilution is then transferred to a sterile Petri dish and mixed with special whey agar. After seventy-two hours' incubation, typical fuzzy lactobacillus colonies develop and the plates are counted.

This method has been found much more reliable than attempts to make serial dilutions in milk and use coagulation as the end point. The colonial characteristics of this organism are such that it is easily recognized in the special whey agar and accidental contaminants can be readily noticed.

The bacterial count of the tablets used on the cases on which our first report was based varied from 10,000 to 100,000. Through improvements in tech-

nique, this has now been raised to one million. In fact, if samples taken from any lot of tablets now show a count below a million, the whole lot is discarded. We stated in 1941 that we had numerous samples taken from different lots of tablets which had been stored in a refrigerator for twelve months without there being any appreciable drop in their bacteriologic count. However, as we did not know how this count would be affected by room temperature, we recommended that the tablets be kept on ice. Further studies since that time seemed to indicate that this was not necessary, but as we are not certain of this, refrigeration is still advised.

We have been especially careful in the accuracy of the claims made as to the number of live lactobacilli present, for we well remember what happened during the heyday of acidophilous therapy. It was then that lactic acid-forming bacilli were used for so many conditions as to be almost considered a panacea for all human ailments. Later, this treatment, falling far short of the claims made for it, fell into disrepute. Probably what played the largest part in causing doctors and patients to lose faith in it was that many of the commercial preparations of earlier days contained few, if any, live lactobacilli.

After making their report in 1941, the authors made no further statistical studies on the efficiency of lactobacillus therapy in trichomonas vaginitis for three years even though they realized that their first publication represented merely a preliminary investigation. However, during this time, we have continued to use the lactobacillus tablets successfully on our private patients. Moreover, the authors continued to receive communication from other doctors in which enthusiasm was expressed for this method of treatment.

Along with these satisfactory reports from other physicians, there are some failures recorded. Doubtless, a few of these might be blamed on the tablets themselves, but many of them were due, in our opinion, to the tablets not being correctly used. These failures have thrown unwarranted doubt on the efficiency of this method of treatment.

It must be appreciated that the bulgaricus bacillus tablets have no antiseptic value. One merely attempts to change the bacteriologic flora of the vagina with them, or rather to restore it to normal so that the trichomonas will no longer be able to survive. To do this, it is necessary that the bulgaricus bacilli which are introduced into the vagina be disturbed as little as possible. Hence, it is definitely wrong to tell the patient to insert the tablets in the vagina in the evening and then take a douche every morning. Another point, that in some instances has not been sufficiently emphasized, is the necessity of continuing the therapy during the menstrual period. This is true for most of the methods of treating this condition, not only for lactobacillus therapy. Lactobacillus tablets must be used while the patient is menstruating.

The method we are advising at the present time is the following: As soon as the diagnosis is made, a bivalve speculum is introduced into the vagina, the cervix inspected for complicating endocervicitis, and Skene's and Bartholin's glands inspected for possible involvement. The vagina is then dried with cotton and two lactobacillus tablets inserted high in the vagina in the posterior fornix behind the cervix. The vaginal orifice is then plugged with a tampon of non-absorbent cotton. When the patient returns on the next day, the tampon is removed, material taken from the vagina for microscopic study, and the treatment carried out on the preceding day is repeated. On this second visit practically every patient will report that the itching has become much less, and it is very unusual to be able to demonstrate organisms at this time.

Such office treatments are repeated daily for five days. The patient is then told to insert two lactobacillus tablets high in the vagina each night. She is told to take douches only if she becomes uncomfortable from unabsorbed particles of the tablets coming out of the vagina and causing irritation. If a douche is used, white vinegar (5 per cent acetic acid) is recommended in a strength of from 2 to 4 tablespoonfuls to 2 quarts of water. Two douches a week are usually sufficient.

This home treatment is continued from two to four weeks and longer if necessary. However, if the organisms promptly disappear and show no immediate tendency to recur, the tablets need be used only every other night. It is especially important that they be used while the patient is menstruating, as that is, of course, the time when the vaginal defenses against the trichomonads are weakest. In a few instances we have had the patient return for a second course of five-day treatments in the office, but this is rarely necessary.

In supposedly cured cases that were unusually long in responding to treatment we advise the patient to insert two tablets into the vagina during the two days before the period, while the flow is on, and for two days afterwards, and to continue doing this for four to six months after she is apparently cured. This probably would be a good routine for all patients, and we have now decided to advise it in every case.

If there is an endocervicitis which in itself is producing some of the leucorrhea it is treated by a cauterization. All patients are given the usual instruction regarding toilet technique, just as should be given no matter what method of treatment is being carried out. This consists of instructing the patient to clean herself, after defecation, from in front backward, that is, from the vagina toward the rectum, rather than in the reverse manner as is usual for most women. This lessens the likelihood of the condition being kept up by constant reinfection from the anus. When it is possible to clear up the infestation quickly, it is better to advise against sexual relations. When the treatment must be continued for a longer period of time, the patient is instructed to take a plain water douche before coitus.

When it is impossible or impractical for a patient to come to a doctor's office or dispensary for a five-day course of treatments, we have had to be satisfied with home treatments carried out by the patients themselves. Some good results have been obtained in this way, although we feel certain that it is easier to re-establish a normal vaginal flora if the physician treats the patient in his office for five days before relying on the patient's efforts. In carrying out the home treatments, the patient should insert two tablets a night high up in the vagina. She should try to place them in the posterior part of the vagina behind the cervix. No douches should be taken during the first week, and, during the second and third weeks, not oftener than every third day and then only if the patient becomes uncomfortable. Treatment should not be discontinued when a menstrual period comes on. Sexual relations should not be permitted during these three weeks. We have not had the patient on home treatment insert tampons to plug the vaginal orifice although this might be helpful. If tampons are advised, they must be made of nonabsorbent cotton, and certainly the vaginal plugs which are used by some women during the menstrual periods should not be used.

This second report of the results of lactobacillus therapy in trichomonas vaginitis is based on the study of 70 patients, all of whom received the five-day preliminary office treatment and then inserted the tablets themselves nightly for at least two weeks at home. Forty-two of the women we treated were private

patients; the rest were seen in the dispensary. Fifteen of the latter group were Negro and 27 were white. As these figures correspond fairly well with the proportion of the white and Negro women seen in the Gynecological Dispensary, this suggests that *Trichomonas vaginalis* vaginitis occurs with equal frequency in both races. The youngest patient in this series was a 10-year-old Negro girl who in addition to the trichomonas infestation had a gonorrheal vaginitis. It was not until after estrogenic suppositories had brought about the disappearance of the gonococci without any appreciable lessening of the leucorrheal discharge that trichomonads were looked for. In our publication of 1941, we mentioned a case of vaginitis due to trichomonads in a 5-week-old child, but in this second series we have not encountered any infestations in infants or young children. Four adult women had gonorrhea as well as the trichomonas infestation and three had both fungi and trichomonads. Fifty-four of the women in our series were married, and 35 had children. There were 16 instances of trichomonas infestations in single women.

All 70 of our patients complained of leucorrhea. Thirty-five, or 50 per cent, gave a definite history of pruritis. Dyspareunia was the outstanding complaint of 15 women. The authors feel so strongly that trichomonas vaginitis is one of the commonest causes of all three of these symptoms, namely, leucorrhea, pruritis, and dyspareunia, that they make it a custom to look for trichomonads as one of the first steps in the study of all women coming to them with one or more of these complaints. The duration of symptoms before the patients came under our care varied from a few weeks to several years. Fifteen had symptoms for over a year. A large portion of patients had been treated unsuccessfully with other methods of therapy.

Wet preparations taken after two weeks of treatment were negative in 64 of our 70 cases and all but three of the women stated that their symptoms had disappeared by that time. Four of the remaining six patients became free of organisms in three months through the continual use of the tablets at home. Two women of the series still have positive smears and leucorrhea, but both feel that they have been greatly helped. We now have 35 women who have reported monthly since cured and who have continued to have negative smears and to be symptomless for a period of six months. Fifty-five have been checked and have remained negative for three months.

Summary

A second series of patients have been treated with tablets containing lactobacilli and the results obtained reported. The method of using these tablets which the authors have found most effective is outlined. It is felt that two factors explain most of the failures that a few physicians have reported with this method of therapy. First, they have recommended daily vaginal douches which defeats the purpose of the method of treatment, and second, they have not insisted that the treatment be continued through the menstrual period. While still not claiming that this method of treatment cures 100 per cent of the cases, the authors feel that their results have been very satisfactory.

The authors wish to take this opportunity to thank Hynson, Wescott & Dunning, Inc., for help in this investigation.

References

1. Brady, L., and Reid, R.: Ann. Surg. 115: 840, 1942.
2. Adair, F. L., and Hesseltine, H.: AM. J. OBST. & GYNEC. 32: 1, 1936.
3. Hesseltine, H.: AM. J. OBST. & GYNEC. 35: 1085, 1938.
4. Karnaky, K. J.: M. Rec. & Ann. 28: 394, 1934.

BENZYL PENICILLIN—CLINICAL TOXICITY AND EFFICACY BY MOUTH IN IMPETIGO IN THE NEWBORN INFANT

A Preliminary Report

THOMAS O. GAMBLE, M.D., LLOYD C. MILLER, PH.D., AND M. L. TAINTER, M.D.
ALBANY, N. Y.

(From the Departments of Obstetrics and Physiology and Pharmacology, Albany Medical College, Albany, N. Y., and Winthrop Research Laboratories, Rensselaer, N. Y.)

IN 1943 Hoerner¹ pointed out the great increase in the load currently being borne by maternity hospitals, especially in the war-industry centers, and cited many factors which have made more difficult the trying problem of controlling impetigo contagiosa of the newborn infant. This affliction constantly menaces every maternity hospital since outbreaks of it are disturbing for several reasons. Not the least among these is the expense of isolating the infected infants, coupled with its attendant demands upon all-too-scarce nursing personnel. Also important is the drain upon the physician's time, both in treating the infant and in allaying the mother whose peace of mind must be preserved.

Since the offending organisms in impetigo contagiosa are considered to be predominantly staphylococci or streptococci, it was natural to try penicillin as soon as it became available. As indicated below, there are already several papers on parenteral injection or local application of penicillin in this condition, but, as far as known, the oral administration of ordinary commercial sodium or calcium penicillin has not been reported. It is the purpose of this communication to record therapeutic success with oral administration of the new benzyl ester of penicillin in a series of 15 babies with impetiginous lesions.

The prospect that penicillin could control impetigo was indicated by Herrell and Kennedy² who reported in 1944 on the general use of penicillin in pediatrics. Their series of cases included one case of extensive impetigo in a 13-day-old infant. Penicillin was given intramuscularly, 2,500 units in 1 c.c. of saline solution, every three hours for two days, at which time "the lesions were completely healed."

Taylor and Hughes,³ working in a British military hospital, were among the first to treat impetigo contagiosa successfully by local application of a penicillin ointment or spray. Relatively small amounts (from 6,700 to 56,000 units used in the course of five to seven days) cured even extensive lesions when applied in these forms. Wrong⁴ has published recently on similar experiences in Canadian military hospitals; using penicillin ointment applied six times daily at first, and later three times daily, he was able to clear the lesions in practically all of 69 cases of impetigo by the third or fourth day of treatment. It was necessary to continue the treatment, however, up to about ten days to prevent the relapses which occurred if medication were suspended as soon as the lesions had cleared.

Cohen and Pfaff⁵ reported experiences in the U. S. Navy with the local application of penicillin in cases of severe impetigo which had not responded to the accepted therapeutic measures, i.e., ammoniated mercury and sulfonamide ointments. These authors point out that the ointment was applied three times daily after removing the crust on the lesions, and observed "most gratifying results" in three to seven days, although the infection had withstood previous efforts at control from three weeks to three months. Templeton, Clifton, and Seeburg⁶ also reported the successful use of penicillin gauze or ointment in 12 cases of impetigo contagiosa.

Intramuscular injections of penicillin sodium in the Albany Hospital had been effective to a gratifying degree in controlling previous outbreaks of impetigo contagiosa in the nursery. However, this form of injection therapy suf-

fers from the disadvantage that the infected skin must be punctured several times daily with a hypodermic needle, thereby offering foci for new infections, and sterile abscesses are occasionally produced. Finally, sterilizing the syringes and needles and frequently preparing sterile solutions of penicillin, made necessary by the latter's instability, take up valuable time. The use of an ointment in these cases was not considered advisable because of the disadvantages of surgical removal of the crust before each application. Therefore, the prospect of using a stable effective oral preparation offered relief from the above listed disadvantages, so inherently associated with parenteral or local administration of penicillin in the forms heretofore available.

The reports of Meyer, Hobby, and co-workers^{7, 8} indicated that while crude preparations of organic esters of penicillin were efficacious orally and parenterally in experimentally infected mice, they were also quite toxic. The benzyl ester of penicillin, which was not studied by these investigators, has been found highly efficacious by us,⁹ and was available in sufficient quantity for clinical trial in a stable, oil-soluble form. Prior to submitting it for clinical use, however, toxicity tests were carried out to determine that it was safe. These tests had just been completed when the opportunity was presented for trying it against impetigo contagiosa.

Toxicity

Several benzyl penicillin preparations have been tested for toxicity on mice, rats, and human volunteers. The benzyl penicillin content of these lots varied between 10 per cent and 50 per cent as estimated by *in vivo* chemotherapeutic assays on mice against a suitable reference standard. The rest of the material was presumably the benzyl esters of the organic acids and other impurities present in crude penicillin.

Hundreds of mice have been given benzyl penicillin in the course of chemotherapeutic tests without apparent evidence of toxic effects, although the doses have often been large in proportion to their body weight.

In rats, sesame oil solutions were used for the toxicity tests. The least pure of these, containing 15 mg. of benzyl penicillin and 135 mg. of impurities per cubic centimeter, was given orally to young growing rats for five days at two dosage levels; 0.2 c.c. daily produced a slight and 0.5 c.c. a marked weight loss. A solution containing 30 mg. per cubic centimeter each of benzyl penicillin and impurities was given orally to four rats for ten days; two each were given 0.5 c.c. and 1.0 c.c. daily, respectively. The smaller dose had no perceptible effect on growth, but 1.0 c.c. retarded growth somewhat, especially during the first three days when the rats ate little food. Growth was resumed by the fourth day and continued steadily to the end of a four-day aftertreatment observation period. Autopsy at this time showed no abnormalities visible upon gross examination. In a chronic test five rats were given 0.5 c.c. of the 50 per cent pure material six times weekly without any change in the growth rate or blood cell picture over an eight-week period. These data indicate that the impurities associated with crude benzyl penicillin are more toxic than the active principle, and that the toxic range of dosage is far beyond any conceivable therapeutic intake.

Twelve volunteers ingested single doses of capsules of 10 per cent pure material in doses equivalent to 10 to 40 mg. of the pure ester. No gastric distress or untoward reaction was reported by any subject, although some noted eructation of a "benzyl acetate odor."

In a special experiment to study the tolerance to benzyl penicillin of a grade of purity readily obtainable in commercial practice, five volunteers took four doses a day for five days by mouth. Each dose contained 50 mg. of the pure ester, a quantity considered to be considerably in excess of ordinary therapeutic requirements. Physical examination of the subjects at the end of the test period showed no change in weight, chest and heart sounds, the systolic or diastolic blood pressure, the gingival mucosa, or the sclera. Blood samples taken before and periodically during the medication were examined for hematocrit, hemoglobin, total red and white cell counts, white cell distribution, nonprotein nitrogen, and icteric index. These examinations gave no evidence of any toxic effect of the benzyl penicillin. Urine specimens were examined daily for glucose, bile pigment, and protein, as well as for casts; the findings were negative but in one subject's urine red blood cells were found consistently

in all specimens except those taken on the first and third days. Three specimens taken three weeks after conclusion of the experiment revealed that this subject regularly excretes a considerable number of red blood cells.*

TABLE I. IMPETIGO CONTAGIOSA TREATED WITH BENZYL PENICILLIN

CASE	AGE (DAYS)	NO. OF DOSES	EXTENT OF LESIONS	CLINICAL COURSE
<i>Propylene Glycol Solution Only</i>				
3-S	19	12	Three lesions on forehead	Lesions slightly improved in 1 day. Repeated treatment on second day; improvement on third and complete healing on fifth day
10-R	8	12	Large lesions on both groins and lower abdomen	Lesions not much improved in 1 day. After 6 more doses, improvement; patient discharged on next day. Four days later lesions almost healed
11-C	8	6	One lesion, 0.5 cm., on buttock	Healed on second day
13-McC	6	6	One lesion, 0.5 cm., on neck	Healed on second day
<i>Propylene Glycol Solution and Oil Solution</i>				
8-B	6	6 (oil)	One lesion, 0.5 cm., on groin originally	After 6 doses in oil, lesions dry and almost healed. Completely healed next day
	13	12 (glycol)	Recurrence 7 days later with 5 new lesions on abdomen and groin. Two days later 3 new lesions on lower abdomen	Recurring lesions treated with benzyl penicillin in propylene glycol; after 6 doses, only slightly improved. After 6 more doses, improved, but upon development of new lesions, gentian violet treatment substituted
14-B	5	6 (glycol) and 6 (oil)	Two lesions, 0.5 cm., on neck	Improved slightly by second day. Six doses in oil given. Completely healed 2 days later
<i>Sesame Oil Solution</i>				
1-M	8	6	Several lesions behind ears and one on groin	Lesions healing and dry 1 day later; completely healed in 3 days
2-W	8	6	Typical lesions, 0.4 cm. in diameter, in axilla	Lesions dry 1 day later and completely healed in 2 days
4-M	3		First lesion appeared on third postnatal day	First lesions cleared after 8 intramuscular injections of 5,000 units each of sodium penicillin in saline
	7	6	Recurrence on seventh day	Recurrent lesions dry and healing 1 day after benzyl penicillin treatment
5-H	8	6	Lesions at angle of jaw and behind ear	After fourth dose, lesions were drying. Discharged almost completely healed after sixth dose. No recurrence at home
6-G	19	12	Extensive lesions on back of neck, shoulders, and head	At end of treatment much improved and by next day lesions healed. Patient had been given 6 doses in propylene glycol 4 days earlier for unexplained fever
7-C	10	6	Lesions on lower lip, 0.5 cm.	Completely healed 1 day later
9-L	13	6	Four lesions, 0.25 cm. in diameter, on each thigh near groin	Completely healed 1 day later
12-E	3	6 6	Two lesions in axilla	Healed in 36 hours Recurrence 4 days after discharge from hospital. Completely cured with 6 doses at home
15-D	6	6	Two lesions, 0.4 cm. in diameter, on head	Healed 1 day later

*The authors are indebted to Dr. R. C. Towse, plant physician of the Winthrop Chemical Company, Inc., for the physical examinations, and to Dr. E. W. McChesney and Mr. Henry Rivenburg, of the Winthrop Research Laboratories, for the urine and blood examinations.

Impetigo

Fifteen consecutive cases of impetigo contagiosa occurring in the hospital nursery were treated with benzyl penicillin (Winthrop) after first being isolated. The material was dissolved in a strength of 25 mg. per cubic centimeter in sesame oil or in propylene glycol; the former is a bland oil commonly used as a solvent for lipoidal pharmaceuticals and the latter is well known as a vehicle for vitamin D. The same dose was used for both preparations, i.e., 0.25 c.c. (10 drops) given every four hours before each regular feeding for a total of six doses in twenty-four hours. Table I summarizes the results according to the vehicle of the preparation used since it was of interest to determine whether either had special merit.

As may be seen from the table, one day of treatment (six doses) was sufficient to clear the lesions in two of the four infants given only the glycol solution, and a second day of treatment (twelve doses) cleared the other two cases. It should be noted that the case 10-R was the worst afflicted of the whole series, and this may account for the necessity of continuing the treatment an extra day. However, the sesame oil solution cured eight out of nine cases in only one day and in these there was a strikingly prompt cessation of the impetiginous process with the beginning of medication. The time required for clinical cure was mainly dependent on the period needed for tissue repair. These facts lent strong support to the impression that the oil solution was the more effective. In none of these cases was there any local treatment of the impetiginous lesions as is necessary when ointments or local antiseptics are applied. Removing the crust is, of course, a very tedious and painful operation, and it is highly desirable that it be avoided. However, the only means of avoiding it heretofore has been the use of parenteral administration of penicillin. This factor by itself would represent a signal advantage in the treatment of impetigo.

Two cases were treated with both the glycol solution and the oil solution. In one of these (14-B) there was slight improvement after one day of the glycol solution, at which time the sesame oil solution was substituted with complete cure in two more days. In the second case (8-B) the oil solution was used first, and completely cured the first attack in twenty-four hours. A recurrence seven days later was treated for two days with the propylene glycol solution, at which time the treatment was complicated by the application of gentian violet by another physician so that benzyl penicillin therapy was discontinued.

The recurrence of impetigo in three of the babies is to be considered a reinfection rather than relapse inasmuch as the lesions were in new body areas. It is not surprising to have recurrences since there is no reason to expect penicillin in any form to confer immunity beyond the time it is excreted. It seems quite probable, however, that a given amount of penicillin taken by mouth as the oil-soluble benzyl ester will not be excreted so soon as if taken parenterally as the sodium salt. This is an important consideration from the standpoint of the prophylactic use of benzyl penicillin. These data give no indication as to how little of the drug might confer a prophylactic protection, although the probability of its effectiveness in this way is clearly demonstrated.

The babies were observed for any untoward reaction to the treatment which might be interpreted as evidence of toxicity. There was no unusual vomiting, failure to gain weight, or any other reaction which would suggest unfavorable effects of the medication.

Summary

The benzyl ester of penicillin given by mouth quickly cleared 16 attacks of impetigo contagiosa in 15 infants in a maternity hospital, and terminated a protracted epidemic. The new form of penicillin is stable at room temperature and can be supplied to the physician ready for use. This material is as effective by mouth in impetigo as is the sodium penicillin administered by injection. The great advantage of being able to give benzyl penicillin orally marks a major advance over the previous injection therapy in handling this difficult condition. The new therapy avoids staining the skin and linen, as in the treatment with dyes, and also does not require the painful surgical removal of crust as is necessary in local therapy of impetigo. The effectiveness of benzyl penicillin demonstrated in this study points out the need for extensive tests of this preparation in other types of infection.

References

1. Hoerner, J. K.: Ohio State M. J. 39: 341, 1943.
2. Herrell, W. E., and Kennedy, R. L. J.: J. Pediat. 25: 505, 1944.
3. Taylor, P. H., and Hughes, K. E. A.: Lancet 247: 780, 1944.
4. Wrong, N. M.: Canad. M. A. J. 52: 341, 1945.
5. Cohen, Theo. M., and Pfaff, R. O.: Arch. Dermat. & Syph. 51: 172, 1945.
6. Templeton, H. J., Clifton, C. E., and Seeburg, V. P.: Arch. Dermat. & Syph. 51: 205, 1945.
7. Meyer, K., Hobby, G. L., and Chaffee, E.: Science 97: 205, 1943.
8. Meyer, K., Hobby, G. L., and Dawson, M. M.: Proc. Exper. Biol. & Med. 53: 100, 1943.
9. Cavallito, C. J., Kirchner, Fred K., Miller, Lloyd C., Bailey, John Hays, Klimek, John W., Warner, William F., Suter, C. M., and Tainter, M. L.: Science 102: 150, 1945.

NAUSEA OF PREGNANCY TREATED BY FORCED HYDRATION

WILLIAM C. ELLER, M.D., AND JOHN H. RANDALL, M.D., IOWA CITY, IOWA

(From the Department of Obstetrics and Gynecology, University of Iowa Hospitals)

SEVERAL clinical entities have acquired the label of "a disease of theories" because of the divergence of opinion as to etiology, the multitude of different—even antagonistic—treatments, and, frequently, the volume of discussion in the literature. Certainly the syndrome of nausea and vomiting of pregnancy qualifies on all the above counts for inclusion in this select group.

In an excellent review of the subject, Hall¹ has shown that everything from an "unstable psyche" to the "presence of tapeworms" has been cited as causal factors. Few, if any, hormones, vitamins, organs, or bodily processes have escaped implication at one time or another.

This addition to the already voluminous writing on the subject is justified on the grounds that the suggested method of treatment combines an effectiveness and a simplicity comparing very favorably with other methods now in vogue.

In deference to those who insist that psychological factors play a predominant role in this condition, may we suggest that nausea and vomiting, though the terms tend to be used almost synonymously, are not one and the same symptom; that the sensation of nausea may have an organic basis, while the presence or absence of actual vomiting depends on the psychosomatic pattern of the patient. It is well known that some individuals are prone to emesis for almost negligible reasons, whereas others may complain of extreme nausea but seem almost unable to vomit without some sort of "assistance."

Although the vomiting, with its resultant dehydration and inanition, is responsible for the serious sequelae, any treatment which completely relieves the nausea will adequately meet the situation. Few, if any, patients will have troublesome vomiting in the complete absence of nausea. Accordingly, treatment was directed solely at the relief of nausea, whether or not accompanied by vomiting.

This treatment was first employed on the assumption that the nausea of pregnancy is the result of the high concentration of chorionic gonadotropin (cyonin) present during the first trimester, and that increased elimination by the kidneys should lower this concentration below a theoretical "nausea threshold" with resultant relief of symptoms. "Forced hydration" has since been

used as the sole treatment of our antepartum patients with symptoms of nausea and/or vomiting.

The following was included in the printed prenatal instructions given to all patients:

Nausea and Vomiting.—It is not necessary to have "morning sickness" because you are pregnant. Only some 50 per cent of pregnant women have these symptoms.

Nausea, when present, is probably due to a hormone secreted by the pregnancy, which circulates in the blood stream and is excreted by the kidneys. This hormone reaches a high level in the blood at about the second month but then decreases in amount, so that by the fifth month you will find that your nausea is relieved or absent entirely.

In the meantime, however, the discomfort and possible dangers of excessive vomiting make effective treatment worth while.

Obviously, if you can make your kidneys excrete this hormone faster than it is being manufactured, its concentration in the blood will fall and your symptoms will be relieved.

This is best done by drinking large amounts of water.

The following plan of treatment is advised as soon as you begin to notice any nausea:

Eat a fairly dry breakfast of toast and jelly, and a dish of dry cereal with a small amount of milk. Eat whatever you desire at other meals.

Between breakfast and lunch drink four glasses of water.

Between lunch and supper drink five glasses of water.

Between supper and bedtime drink six glasses of water.

This will not mean drinking a glass of water oftener than every half hour; you should be able to do this easily. Increasing the amounts toward the end of the day relieves you of drinking so much in the morning when your discomfort is apt to be worse. If you are most nauseated in the evening, reverse the schedule.

This program will necessitate your getting up in the night to urinate, but you will be doing this anyway; drink a glass of water each time you get up.

This treatment will seem difficult, especially if you have already started vomiting. If the first few glasses are vomited, repeat them immediately and count only the glasses retained.

In a day or so you will find that your urine is almost colorless. This is the only way of being sure that you are drinking enough water. You may find that very hot or salt water is more easily retained.

You can be assured that as soon as your urine becomes clear, your nausea will improve and shortly will disappear altogether.

This rather lengthy discussion of theory and detailed plan of treatment was written after analysis of early failures. It soon became apparent that it is not sufficient to tell the patients to "drink lots of water"; this, to the average woman, means seven or eight glasses a day. Or, when told to drink fifteen glasses of water daily, the first reaction of the patient, especially if she had begun to vomit, was, "I can't do it." The simple expedient of furnishing the patient some explanation of the treatment and a definite schedule to follow gave immediately improved results.

It should be emphasized that these patients tend to recover spontaneously at about the fourteenth to sixteenth week of gestation. Accordingly, great care must be exercised in evaluating the results of any treatment, however effective, at or after this period.

Material and Results

Sixty-eight antepartum patients with symptoms of nausea and/or vomiting were studied as to results of this treatment. The following criteria were established in evaluating these results:

Very Satisfactory.—Complete relief of nausea in four days or less, the patients being less than three and one-half months pregnant at the time of relief.

Satisfactory.—Complete relief of nausea in ten days or less, the patients being less than three and one-half months pregnant at the time of relief.

Fair or Doubtful.—Relief in more than ten days, or relieved when more than three and one-half months pregnant.

Poor.—No relief because of inadequate treatment.

Very Poor.—No relief in spite of known adequate treatment.

Table I lists the results of treatment according to the above criteria.

TABLE I

RESULTS	NO. OF CASES	PER CENT
Very satisfactory	32	47.0
Satisfactory	10	14.7
Fair or doubtful	16	23.5
Poor	6	8.8
Very poor	4	5.9
Total	68	100.0

All but one of the patients in the *Satisfactory* group were relieved in one week. In other words 60 per cent of the patients treated were relieved in seven days or less, at a time in their pregnancy when they might have expected to still have troublesome symptoms. Five of these patients volunteered the information that their vomiting stopped after the first day of treatment. Once relief was obtained, several patients were able to maintain relief on less than the prescribed amount of water. But one patient who was relieved after two days on fifteen glasses, cut the amount to eight glasses, with prompt return of her symptoms; she went back to drinking fifteen glasses and had no further trouble. Another patient obtained a clear urine and rapid relief of her nausea on twelve to sixteen glasses daily; then the water seemed to make her nauseated; she cut her intake to nine to ten glasses and remained asymptomatic.

All the patients having *Fair or doubtful* results were relieved of their distress, but seven required more than ten days to obtain relief, while nine were not relieved till after three and one-half months, so that the treatment cannot be given credit for the results. Six of this latter group, however, did not start treatment till after three and one-half months.

All of the six patients who did not receive adequate treatment were cases early in the series who had been told simply to drink "lots of water" or "fifteen glasses of water a day." None of them drank more than ten glasses.

Four of the patients were known to have had adequate treatment over a sufficient period of time and were completely unrelieved of their symptoms. One of these was still nauseated and vomited occasionally at five months. Two were relieved by parenteral vitamin B complex. The fourth had marked nausea without vomiting associated with marked gaseous abdominal distention; this was found to be definitely related to starches and carbohydrates in her diet, and was relieved in two or three days by administration of Taka-Diastase and mild catharsis.

Discussion

Corresponding closely to the period of greatest syncytial activity, the serum concentration of chorionic gonatropic hormone (cyonin) rises rapidly from its inception to a peak at about the thirtieth day of pregnancy. Cyonin production may, during this period, rise to as high as 1,000,000 rat units per day in a normal pregnancy. This peak is shortly followed by an equally abrupt decline to a level of less than 10,000 rat units per day, which concentration is maintained throughout the duration of the pregnancy.²

Hall cites the work of Brindeau et al.,³ who demonstrated high serum and low urine concentration—retention, perhaps?—of cyonin in cases of hyperemesis, with return to normal levels on recovery from the vomiting.

Schoeneck⁴ presents evidence of abnormally high levels of cyonin in both the urine and serum of patients with nausea and vomiting, also points out that the greatest concentration occurs at the time when nausea and vomiting are most commonly encountered. It may be added that the fall in cyonin concentration coincides with the time when these patients tend to be spontaneously relieved of their distress.

It is probably significant that in hydatidiform mole, with its sustained high levels of serum and urine cyonin, nausea and vomiting are more excessive than in normal pregnancy. Excessive vomiting was noted in 13.5 per cent of the 500 cases reported by Palmer Findley.⁵

While the above considerations led us to initiate this therapeutic approach to the problem, these results should not be construed as additional evidence that cyonin is the proved cause of the nausea of pregnancy. It is entirely possible that some other metabolite is actually responsible, and that it was so altered or excreted by the treatment as to give these favorable results.

The etiological implications might have been clarified had the serum and urine concentrations of cyonin before and after treatment been studied. Further, the production of nausea by administration of large amounts of the hormone to pregnant and nonpregnant women would have been significant. These investigations were not possible at the time of this study.

Nevertheless, regardless of our present ignorance as to the exact mechanism involved, the clinically significant fact remains that this method of treatment, properly conducted, will completely and rapidly relieve nausea in the majority of pregnant women. For its simplicity, economy, and effectiveness, it merits an important place in our therapeutic armamentarium.

Summary

1. "Forced hydration" with its resultant diuresis was used as a means of treating nausea of pregnancy, whether or not accompanied by vomiting.
2. Specific directions for the patient, preferably printed, give improved results.
3. Results of any treatment obtained after three and one-half months' gestation are misleading.
4. Sixty per cent of the patients treated were completely relieved of nausea within seven days; 47 per cent were relieved within four days.
5. There is evidence that the nausea of pregnancy follows and is due to the high serum concentration of chorionic gonadotropin (cyonin) in the first trimester of pregnancy; reduction of this concentration by diuresis may explain the effectiveness of this treatment.
6. This method of treatment deserves recommendation because of its simplicity, economy, and effectiveness.

References

1. Hall, M. B.: *Am. J. M. Sc.* 205: 869, 1943.
2. Evans, H.: Quoted in Davis' *Gynecology and Obstetrics*, Hagerstown, Md., 1938, W. F. Prior Co., Inc., Vol. II, Chap. 3, p. 34.
3. *Ibid.*¹
4. Schoeneck, F. J.: *AM. J. OBST. & GYNEC.* 43: 308, 1942.
5. Findley, P.: Quoted in Davis' *Gynecology and Obstetrics*, Hagerstown, Md., 1938, W. F. Prior Co., Inc., Vol. I, Chap. 13, p. 5.

SUPPURATING FIBROMYOMAS: REPORT OF A CASE WITH A REVIEW OF THE LITERATURE

IRVIN MILLER, B.S., M.D., NEW ROCHELLE, N. Y.

(From the Departments of Gynecology and Pathology, Jewish Hospital of Brooklyn)

SUPPURATION of fibromyomas is rare. A survey of the literature reveals that a suppurating fibromyoma associated with prolapse of the uterus has never been reported. Because of its rarity and the paucity of literature upon the subject, this case is presented.

Report of a Case

M. N., No. 271536, a 51-year-old West Indian Negro woman was admitted on Jan. 6, 1944, to the Gynecological Service of the Jewish Memorial Hospital with complaints of abdominal swelling and a protruding mass at the vagina.

The patient was a gravida iii, para i, the last pregnancy having occurred thirty years prior to admission. She had been a sufferer from "high blood pressure" for six years and stated that she had been told that "her heart was bad." The last menstrual period had occurred one and one-half years previously.

The patient had first noticed the protrusion at the vulva two years before admission. It was associated with a sense of heaviness and bearing-down pelvic pain. An abdominal mass was noticed one year before admission, and two weeks before the patient entered the hospital it had suddenly increased in size. With the increase in size the patient began to experience fever, malaise, chills, and nausea. An episode of vaginal bleeding during which an estimated glassful of bright red blood was lost had occurred sixteen days before admission. Because all symptoms were becoming worse, the patient applied for admission.

Physical examination on admission revealed an emaciated Negro woman appearing much older than the stated age, and in acute distress. The temperature was 101.8° F., the pulse 94, and respirations 20. The mucous membranes were pale. The blood pressure was 170/110. The heart was found to be much enlarged, the apex beat being placed in the sixth interspace in the anterior axillary line. The lungs were clear. Abdominal examination revealed an ovoid tumor measuring about 35 by 25 cm. The tumor arose from the pelvis, filled both flanks, and reached to the level of the umbilicus. Its upper and left portions were cystic. The mass was relatively fixed and somewhat tender to palpation.

Vaginal examination revealed a third-degree prolapse of the uterus with complete eversion of the anterior and posterior vaginal walls, the cul-de-sac, and complete descensus of the bladder. After replacement of these structures, the uterus was thought to be palpable as a small senile structure lying on the left and anteriorly.

Laboratory Findings.—The hemoglobin was 55 per cent and red cells 3,450,000; white cells 38,700, with 91 per cent polys, 1 per cent immature forms, 7 per cent lymphocytes, and 1 per cent eosinophiles. Toxic granules were noted in the polys, and there was achromia of the red blood cells. The Wassermann and Kline tests were 4 plus positive. The urine was acid, negative to albumin and sugar, and was negative microscopically. A dilution and concentration test revealed the highest specific gravity to be 1.1014 and the lowest to be 1.004. The blood urea nitrogen was 11 mg. per cent, the blood sugar 113 mg. per cent, and the total proteins 5.95 Gm. per cent. X-ray studies revealed an enlarged boot-shaped heart and the abdomen enlarged by a soft-tissue mass which almost completely filled the pelvis and extended upward to above the crest of the ilium. Electrocardiogram revealed marked left axis deviation and mild myocardial damage. The erythrocyte sedimentation rate was 98 mm. (normal in females 20 mm.).

Clinical Diagnosis.—Pseudomucinous cyst of the ovary with infection; complete prolapse of the bladder, uterus, and cul-de-sac; hypertensive cardiovascular disease; secondary anemia.

Course.—For the first four days in the hospital the patient's temperature fluctuated between 101° and 102.8° F. Blood cultures were repeatedly negative. On the fifth hospital day, because of the obviously severe infection, sulfadiazine therapy was begun, with a rapid attainment of a high blood level of the drug. On the ninth hospital day the temperature had subsided to

levels between 100° and 101° F. On this day, however, the patient began to have nausea, vomiting, and diarrhea, and for the first time since admission began to complain of severe abdominal pain of a colicky nature. Examination revealed that the mass now reached to the level of the xiphoid, a rise from the level on admission of about 6 cm. The patient was obviously failing. Though her condition for operation was extremely poor, a laparotomy was decided upon. Medical consultation confirmed this opinion. Accordingly, on the tenth hospital day an exploratory laparotomy under cyclopropane, oxygen, and curare anesthesia was performed. The uterus was found to be enlarged to the size of a full-term gestation, the enlargement being primarily due to a large fibromyoma that occupied the fundus and upper part of the corpus uteri and measured 15 cm. in diameter. At the top of this tumor a defect 9 cm. in diameter was present. The defect was closed by adherent indurated omentum. On separating the omentum from the uterus in the course of the operation, the fibroid was found to be cystic, containing 950 c.c. of thick creamy pus. The pus was lemon-yellow in color and odorless. Four other intramural fibroids ranging in diameter from 5 to 9 cm. were noted in the uterus. No free peritoneal fluid was found. The tubes and ovaries were normal in appearance. A specimen of the pus was taken for culture, and then a supracervical hysterectomy with bilateral salpingo-oophorectomy was done. Ten grams of sulfanilamide were dusted into the peritoneal cavity. The peritoneal cavity was drained from the lower angle of the wound with a rubber Penrose drain.

After operation the patient's condition was good for eight hours. In the ninth hour postoperatively her blood pressure suddenly fell, and despite all forms of therapy, including parenteral digitalis and sulfadiazine, she expired thirty-four hours after operation.

Culture of the pus from the suppurating fibroid revealed *Streptococcus hemolyticus*.



Fig. 1.

Gross Description of Specimen (Fig. 1).—The specimen consisted of a grossly misshapen uterus, amputated above the cervix and measuring 17 by 16 by 10 cm. Firm nodules up to 9 cm. in diameter, composed of gray and white fibers, projected from the serosal surface. At the fundus was a large, firm nodule, intramural in location, that measured 15 cm. in its greatest diameter. At its upper surface was a defect 9 cm. in diameter. The upper two-thirds of this nodule consisted of a cyst containing soft, friable, necrotic, gray, brown, and pink tissue. Scattered throughout the remainder of the nodule were soft, necrotic areas measuring up to 4 cm. in diameter. The uterine canal was distorted and measured 8 cm. in length.

Microscopically (Fig. 2) the endometrium revealed infiltration with small round cells, large mononuclear cells, plasma cells, and some polys. Within the myometrium, foci of similar infiltration were seen.

The nodules were revealed to have necrotic, poorly staining, loosely arranged tissue with infiltrations of mononuclear and polymorphonuclear cells. In some places the infiltration of these cells completely obliterated the cyto-architecture.

Sections from normal-appearing myometrium adjacent to the necrotic fibroids revealed foci of dense infiltration with polys and monocytes.

Pathologic Diagnosis.—Leiomyoma of uterus, with chronic and acute suppurative reaction; endometritis and myometritis, chronic and acute; omentum with acute suppurative inflammatory reaction. Autopsy revealed the cause of death to be acute generalized peritonitis. Other postmortem findings of note were multiple gallstones and a markedly enlarged heart.



Fig. 2.

Review of the Literature and Discussion

Incidence.—Distinction between fibromyomas that are necrotic, gangrenous, or subject to some other marked degenerative change, and those that are truly suppurating is rarely made. Also, distinction between fibroids infected primarily from the uterine cavity and those secondarily infected from without the uterus is not made. True suppurating fibromyomas, if one excludes those of submucous location (and therefore in direct contact with potentially or actually infected cavities), are extremely rare. It can also be said that even submucous fibroids, the type which most frequently show suppurative changes, evidence these changes mostly in the mucosa overlying them rather than in the substance of the tumor itself.¹

A review of the literature from 1871 to the present attests to the rarity of true suppurating fibromyomas; there are less than 75 cases reported. Carter² in 1871 apparently made the first recorded reference to a suppurating fibroid in reporting a case before the London Obstetrical Society. Guery³ in a review of the literature up to 1901 was able to collect but 47 cases of suppurating tumors not associated with other types of infectious degeneration. Messa⁴ in 50 cases, Le Bec⁵ in 57, and Noble⁶ in 218 failed to observe suppuration. Harris⁷ in describing unusual complications of fibroids in a large series of cases does not mention suppuration. Lauvers⁸ reported an incidence of 0.5 per cent in 360 cases. Kelly and Cullen⁹ in 1,674 fibroid cases noted suppuration in 13

cases, two of which were from the practices of other gynecologists. Nixon,¹⁰ in reporting a case, notes that it was the first case of suppuration seen by Deaver in over 1,200 cases of operated fibroids. A review of over 1,400 operated fibroid cases in the Brooklyn Jewish Hospital during the last fifteen years failed to reveal a single case of true suppuration.

On the other hand, some authors state that suppuration is not uncommon. Stark¹¹ reports three cases of suppuration associated with red degeneration that occurred within a short period of time. Martin¹² reports a 5 per cent and Collingworth¹³ a 15 per cent incidence of suppuration. However, the last two authors do not differentiate between true suppuration and infectious degeneration.

Mode of Infection.—Fibromyomas become infected in two ways, i.e., primarily by extension from the uterine cavity, or secondarily by extension from adjacent or contiguous structures. Kelly and Cullen⁹ noted the following modes of infection in 13 cases: 3 by direct continuity with the bowel; 6 from the uterine cavity (evidenced by lymphangitis and endometritis); 4 with no demonstrable mode of infection. Stark reports of his cases as being infected from acute pelvic inflammatory disease. All tumors that are infected by spread from contiguous structures (bowel, adnexae, etc.) are subserous in location. However, tumors of this situation can also be infected from the uterine cavity.

Other modes of infection have been suggested. Boyd,¹⁴ Gardner,¹⁵ Graves,¹⁶ and others¹⁷ feel that one probable route of infection is a hematogenous one superimposed on a *locus minoris resistentiae*, the locus being the result of hyaline or other types of degeneration. Wolfe,¹⁸ on the other hand, feels that the almost universal degenerative changes seen in fibroids are due to a disturbed blood supply of the tumors and, accordingly because of the rare incidence of infection, feels that hematogenic spread is an improbable route.

The routes of infection in order of frequency are: (1) lymphatic spread from the endometrial cavity; (2) direct extension from bowel, infected adnexae, and other contiguous structures (this in subserous tumors only); (3) hematogenous spread from circulating organisms to a local point of lowered resistance.

In the case presented in this paper, the route of infection lay from the endometrial cavity. An unusual feature was the infection of the uterine cavity resulting from the exposed and vulnerable situation of the prolapsed uterus.

Pathologic Characteristics.—No one type of organism predominates as the infectious agent. Colon bacilli, streptococci, and staphylococci are the most common infecting organisms. Nixon's case was caused by gonococci. This is the only case reported with this type of organism. No case of gas bacillus infection was found in the literature.

The amount of pus contained in the tumors tends to be large. The average amount in the cases in the literature was about 500 c.c. Kelly and Cullen had cases containing 1,900 and 1,650 c.c. of pus. Vautrin¹⁹ reported a case containing 2,500 c.c.

The pathologic picture, gross and microscopic, is the characteristic one of acute suppurative inflammation. Very frequent is a contiguous inflammation of peritoneum and omentum.

Complications, due to progression of the inflammatory process, are common. Rupture into the peritoneal cavity with production of acute generalized peritonitis,²⁰ perforation into the bowel with tenesmus, diarrhea, etc.,²¹ and perforation into the uterine cavity with production of a foul, profuse vaginal discharge,²⁴ are reported. Rupture into the bladder has been reported once.²³

Age Incidence, Symptoms, Diagnosis.—The greatest age incidence of suppuration occurs during the sexually active period of life, i.e., 19 to 46 years. While a large number of cases occur in puerperal women, there is no specific age level nor is there a relationship to the number of children a woman has had.

Symptoms are marked, being essentially those of acute infection. The erythrocyte sedimentation rate is increased and a leucocytosis is usually present. There is usually rigidity and tenderness of the anterior abdominal wall. A characteristic symptom is a sudden increase in size of the fibromyoma associated with sharp lancinating pains in the affected region.⁹ Symptoms of acute peritonitis and gastrointestinal upset occur, depending on the subsequent spread of the infection.

The diagnosis, while not difficult to make, is nevertheless rarely made, apparently because of the extreme rarity of this complication of fibroids. Kelly and Cullen, in their series of 13 cases, had 4 not diagnosed before operation. Stark's series of three had one not diagnosed.

Treatment and Prognosis.—The treatment is surgical. Supracervical hysterectomy done as quickly as possible is the method most frequently used.

The prognosis with the above treatment is extremely poor. Kelly and Cullen had a mortality of 4 in 13 cases. One of 3 cases died in Stark's series. Basso²⁴ estimates a 50 per cent mortality in suppurating fibromyomas. Where they are given elsewhere^{25, 26} in the literature, mortality rates range from 33½ to 70 per cent. This grave prognosis associated with extirpation of the uterus causes us to feel that simple drainage with later extirpation when the patient's general condition is better might give better results.

No mention is made of the effect of sulfonamides and penicillin on these cases. In all probability better results will be obtained with their use.

Summary

A case of suppurating fibromyoma associated with complete prolapse of the uterus has been presented. Ascending infection is proved. Treatment is reviewed. Prognosis is grave.

Thanks are extended to Dr. S. A. Wolfe for his suggestions and help in the preparation of this paper.

References

1. Ewing, J.: *Neoplastic Diseases*, Philadelphia, 1936, W. B. Saunders Co.
2. Carter, S.: *Tr. Obst. Soc. Lond.* 13: 167, 1871.
3. Guery, A.: *Study on the Suppuration of Uterine Fibromyomas*, These de Paris, 1901.
4. Messa, G. E.: *Ann. di ostet.* 2: 549, 1912.
5. Le Bec, S.: *Suppurating Fibromyomas*, These de Paris, 1905.
6. Noble, C. P.: *Brit. Gynaec. J., Lond.* 17: 170, 1901-1902.
7. Harris, L. C., et al.: *South. M. J.* 31: 968, 1938.
8. Lauvers, A. D.: *Bull. Soc. belge de gynéc. et d'obst., Brux.* 9: 49, 1897.
9. Kelly, H. A., and Cullen, T. S.: *Myomata of the Uterus*, Philadelphia, 1909, W. B. Saunders Co.
10. Nixon, J. W., Jr.: *J. A. M. A.* 75: 251, 1705, 1920.
11. Stark, M. M.: *Am. J. Surg.* 4: 83, 1939.
12. Martin, C. M.: Cited by Guery.
13. Collingworth, C. J.: Cited by Guery.
14. Boyd, Wm.: *Surgical Pathology*, Philadelphia, 1942, W. B. Saunders Co.
15. Gardner, G. H.: *Nelson Looseleaf Surgery*, New York, 1927, Thos. Nelson & Sons, Vol. 7.
16. Graves, W. P.: *In Curtis, Obstetrics and Gynecology*, Philadelphia, 1926, W. B. Saunders Co.
17. Lynch, F. W.: *Pelvic Tumors, Gyn. & Obstet. Monographs*, New York, 1926, D. Appleton-Century Co.
18. Wolfe, S. A.: Personal communication.
19. Vautrin, C.: *Rev. méd. de l'est.* 40: 479, 1908.
20. Buman, C.: *Rev. méd. de la Suisse Rom.* 48: 27, 1928.
21. Kjaer, M.: *Nord. med. (Hospitalstid)* 8: 1802, 1940.
22. Oliveira, S. A.: *Bahia Med.* 3: 207, 1932.
23. Delage, J., and Gangoux, F.: *Gaz. d'hôp.* 80: 591, 1907.
24. Basso, G. L.: *Ginecologia, Firenze.* 11: 1914.
25. Rinesi, R.: *Semana méd.* 1: 920, 1925.
26. Nisat, E.: *Bruxelle Med.* 7: 593, 1929.

Additional References

27. Kosmak, G.: *New York State J. Med.* 20: 259, 1920.
28. Darnall, W. E.: *New York M. J.* 116: 17, 1922.
29. Stein, H. E.: *J. A. M. A.* 81: 1783, 1923.
30. Goinard, E.: *Rev. franç. de gynéc. et d'obst.* 16: 43, 1931.
31. Blacker, E.: *Tr. Obst. Soc. Lond.* 49: 100, 1907.
32. Bonfils, E.: *Contribution à l'étude de la Suppuration Fibromes*, These de Montpellier, 1910.
33. Van Orden, B.: *Am. J. Obst.* 68: 99, 1913.
34. Berger, G.: *Suppuration des Fibromes au Cours de la Puerperalitie*, These de Paris, 1907.
35. Michon, G.: *Gynecologie* 14: 9, 1910.
36. Hartmann, B., et al.: *Ann. de Gyn. & Obst.* 45: 425, 1896.
37. Bengolea, A. B.: *Bul. Soc. de Obst. & Gynec.* 9: 355, 1942.

PARACERVICAL ANESTHESIA FOR THE RELIEF OF LABOR PAINS

SAMUEL S. ROSENFELD, M.D., NEW YORK, N. Y.

(From the Department of Obstetrics, Jewish Memorial Hospital)

HAVING performed such gynecologic operations as dilatation and curettage, amputation of the cervix, repair of the cervix, the Manchester operation, the interposition operation, and even vaginal hysterectomy under paracervical anesthesia supplemented by local infiltration and at times by rectal ether, it seemed to me that this form of anesthesia should prove effective in obstetrics. I therefore tried it and when the very first case proved satisfactory, I was encouraged to continue.

In a study of the literature, I found that Gellert,¹ in 1926, reported a series of thirty cases, terming his method "parametran." His technique consisted of injecting 10 c.c. of a 1 per cent solution of novocain parametrically on both sides into the cervical plexus. Pribram² reported a series of cases in 1927, citing the above-mentioned work of Gellert. He called his method "blocking of the uterovaginal plexus." His anesthetic agent was 1 per cent novocain-suprarenin solution. Henriet,³ in 1937, reported a technique for infiltration of the "pelvi-perineal plexus" using 20 c.c. of 1 per cent novocain solution without adrenalin. Henriet and Valdejo⁴ used this method in 85 obstetric cases with success and speak of infiltrating the pelvi-perineal plexus in its paravaginal and paracervical portions.

In this form of anesthesia, the local anesthetic is injected alongside the cervix, the aim being to anesthetize and thus block the sensory nerve fibers in the parametrium. This is easily accomplished by a bilateral injection of the anesthetic solution parallel to and alongside the cervix to a depth of from 3 to 4 cm. into the lateral fornices.

In the beginning, I attempted to expose the cervix and inject under direct vision, employing one and sometimes two assistants. This technique proved unsatisfactory, first because patients frequently complained of pain caused by traction on the retractors, and second, it commandeered the time of interns who were urgently needed elsewhere in the hospital. I soon found that one could more readily and more easily inject the patient by himself, relying on the sense of touch. The materials required are a 10 c.c. syringe, a long flexible needle, and the anesthetic solution. If desired, a needle constructed with a shoulder such as is commonly used for injections about the tonsils may be employed, the shoulder limiting the depth of the needle's penetration into the parametrium.

Method

When ready to inject the solution, the patient is prepared and draped as for delivery. To conserve supplies, I have had a bundle made up known as a "paracervical bundle" containing 4 towels, leggings, 1 sheet, 1 Asepto syringe with rubber bulb, 2 medicine glasses, a 10-c.c. syringe, and a long flexible needle.

After the patient has been washed with soap and water and sprayed with merthiolate solution, she is draped. An Asepto syringe full of aqueous merthiolate is injected into the vagina. I usually begin by injecting the left side first. The index and middle fingers of the left hand are pressed into the space between the left side of the cervix and the vaginal vault, and the needle is guided so that it pierces the vault close to and parallel to the cervix. This procedure is then repeated on the right side.

I began by using novocain. I found, however, that the anesthetic action as a rule lasted only a short time, though in a few instances periods of from one to two hours of complete relief from pain were observed.

In an effort to secure more prolonged anesthetic action, resort was made to nupercaine (alpha-butyloxyinchoninic acid diethylethylenediamide hydrochloride). Solutions of 1:2,000, 1:1,500 and 1:1,000 were all used with very satisfactory results. We also employed Eucupin (isoamylhydrocupreine dihydrochloride) with equally satisfactory results.

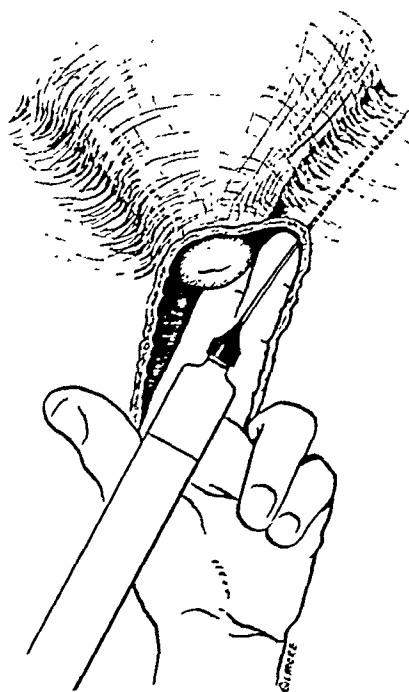


Fig. 1.—Injection of left parametrium. The right side is injected in the same manner using the same hand. The position of the needle indicates the outer limit of the area injected. Most of the anesthetic solution is injected much closer to the cervix.

Results

This series consisted of 100 patients of whom 45 were nulliparas and 55 multiparas.

All of the anesthetic agents employed were effective. Every patient, without exception, enjoyed relief from pain, analgesia frequently being noted even before the completion of the injection. When less than 50 c.c. of solution were injected, the duration of anesthesia was appreciably less than when larger amounts of the same agent were employed.

Both nupercaine and Eucupin were much more effective than novocain from the standpoint of duration of anesthesia. Nupercaine 1:1,500 was as effective as the 1:1,000 solution and more effective than the 1:2,000. The higher concentrations of Eucupin were more effective than the standard or stock solution (Eucupin dihydrochloride 0.06 Gm., procaine hydrochloride 0.3 Gm., Ringer's solution q.s. ad 30 c.c.). The longest duration of anesthesia, eight hours and six hours, respectively, was observed in two patients who were injected with 0.5 per cent Eucupin plus 1 per cent procaine and adrenalin.

One patient in the 1:1,500 nupercaine group had five hours of complete relief from pain.

An attempt to determine the average duration of anesthesia in each group studied yielded inconclusive data because the patients were not injected at exactly comparable times and in many instances labor was completed at various intervals before the anesthetic action of the various injected solutions would have disappeared.

When injecting novocain, one-half to two hours of anesthesia was obtained depending on the concentration of the solution. The nupercaine cases enjoyed two and a half to four hours complete relief from pain when 50 c.c. or more of a 1:1,500 solution was injected and about the same length of analgesia when the standard solution of Eucupin was employed. Stronger concentrations of Eucupin gave from two and a half to five hours of complete relief and occasionally exceeded the latter figure.

In most patients it was observed that the period of complete relief was followed by a longer or shorter period of partial relief, during which time the patient sensed pain but stated that it "wasn't bad." If no more solution was injected and labor continued, the intensity of the pain would increase so that eventually the labor pains would be "as bad" as before the injection.

There did not appear to be any effect on the average length of labor. Here and there a case appeared to us to have been prolonged by the use of the anesthetic solution but this was compensated for by cases that seemed to be hastened when a similar solution was injected.

Our series is not yet large enough to permit us to determine whether adrenalin increases the duration of the anesthetic effect of the injected solutions or whether it has any effect on prolonging or shortening the duration of labor.

It was noted in the vast majority of cases that when the presenting part reached the perineum, pain would return. In the last few cases of this series, we have been able to obtain a more or less painless perineal stage by local infiltration of the posterior portion of the vaginal vault, injecting laterally to the midline so as to avoid puncturing the rectum.

In the cases where the blood pressure was studied there was only one instance where a marked drop of blood pressure was noted. The pressure prior to injection was 130/80 and immediately after it fell to 80/60. There were no clinical symptoms, the patient was unaware of the condition, and in fifteen minutes the pressure had returned to its former level. In this case the anesthetic solution was 0.4 Eucupin with procaine. The fetal heart rate became appreciably lower in two cases immediately after injection. This condition lasted only a very short time and both infants were born alive, and left the hospital in good condition, despite the fact that one of them was suffering from erythroblastosis. In one instance 1:1,500 nupercaine with adrenalin was used, and in the second case 1:1,000 nupercaine with adrenalin.

There was no maternal mortality.

Complications were very few in number. One patient had a severe postpartum chill immediately following delivery. The temperature remained elevated for forty-eight hours. The solution used in this case was Eucupin. One patient developed a marked postpartum distention. This patient was also injected with Eucupin. The distention disappeared after seventy-two hours.

One infant was stillborn. The mother received one injection of nupercaine 1:1,500 and had about three hours relief from pain. The fetal heart sounds at this time were normal and remained so until just before delivery about eight hours after the injection, at which time the anesthetic effect had long since disappeared. Delivery was accomplished by midforceps and there was a very tight coil of umbilical cord tightly wound around the neck. All attempts at resuscitation failed. Permission to perform an autopsy was refused.

In two instances emergencies arose after paracervical injections had been made, necessitating cesarean section. The mothers and babies progressed favorably.

Some of the associated conditions encountered were chronic cardiac disease, multiple fibroids, psychoneurosis, and hyperthyroidism. All these patients were injected without complication and with evident benefit. An infant suffering from erythroblastosis was born to one of the mothers in this series. The diagnosis was proved. Prompt and rigorous treatment was instituted; the baby recovered and left the hospital in good condition about one month after birth.

In a few instances, contemplated injections were cancelled because the presenting part had dilated the cervix to such an extent that it would have been impossible to reach the paracervical tissues without danger of injecting some of the anesthetic solution into the fetal scalp.

In a few cases only one side could be safely injected and these patients enjoyed a great measure of relief.

A few patients, immediately after or while the injection was going on, complained of an initial tingling in the legs and toes followed by numbness. This syndrome cleared up in every instance before the patient left the delivery room. One patient who was injected with novocain became "giddy." This lasted for only a few minutes. One patient complained of severe pain in one heel, the pain lasting about twenty-four hours.

Practically all of the patients, even the most boisterous, became calm and cooperative immediately after the injection.

Uterine contractions continued in every case. The patients had no sensation of pain, and multiparas, fully or almost fully dilated, were urged to bear down when a uterine contraction was observed. The patients cheerfully complied and it was noted that the expulsive efforts were far more effective in these patients than in those who sensed pain. When pituitrin was injected intramuscularly, the uterine contractions were seen to be much stronger and more frequent. The patients, however, were unaware of this and felt no pain.

Spontaneous delivery occurred in 22 per cent of the nulliparas and in 69 per cent of the multiparas. Many of the forceps deliveries were of the so-called prophylactic type. The anesthesia employed to effect delivery included local infiltration plus pudendal block, combined anesthesia, i.e., inhalation plus local infiltration anesthesia as is described by the author,⁵ and spinal.

Discussion

It is a moot question as to whether or not the relief of pain in labor is so important as to justify the amount of research and thought that has lately been applied to this problem. The future will answer that question for us.

Clinically, it does not appear to make much difference whether the relief of pain is procured by drugs acting directly on the central nervous system or whether analgesia is obtained by action on the local nerves.

Since drugs acting on the central nervous system are so much more easily administered, it therefore appears logical to make use of them first and when their action is satisfactory, local measures need not be instituted.

In cases where centrally acting drugs fail to give the required relief, paracervical approach has much in its favor. There is no difficulty in injecting the drug solution into the proper channel. In not a single instance in this series did the injected solution fail to give relief, indicating that the drug had been injected in the proper area in every case. This contrasts with the 10 to 15 per cent of reported failures with caudal due to inability to inject the drug into the proper space.

In the average multipara the paracervical method when it is indicated is almost ideal. The labors as a rule are short and most of the anesthetic solutions used produce anesthesia that is effective through the most painful part of parturition. The same holds true for nulliparas in whom the cervixes are soft and the fetus is of average size. In these women, labor is likely to be shorter than the average for nulliparas. If the injection or injections are properly timed, the most painful portions of the labor could be eliminated.

As stated above, 69 per cent of the multiparas and 22 per cent of the nulliparas delivered spontaneously. This contrasts with the almost universal need for instrumentation when caudal anesthesia is used.

Caudal enjoys certain advantages over paracervical. When continuous caudal is used, there is, of course, no need for reinjection. When using the paracervical approach, reinjection is necessary when pains reappear if one desires to have the labor continue painlessly. Should operative procedures become necessary to terminate labor, one can proceed without delay when using caudal, whereas, with paracervical, additional anesthetic procedures, e.g., local infiltration, pudendal block, inhalation, or spinal, are necessary. Caudal has another advantage in that, when it is successful, the perineal stage is painless. With the paracervical method, the level of anesthesia is higher than the perineum, and as a result the perineal stage is usually painful. However, in the last few cases in this series, infiltration of the vaginal wall and posterior vagina have succeeded in securing a practically painless perineal stage. In the average multipara, the perineal stage lasts only a very short time, and the pain can easily be controlled by either local infiltration of the perineum or a few whiffs of either nitrous oxide or ether administered during the course of the pain.

Table I shows the drug agents employed in this series. Procaine was the first anesthetic drug used and while it was just as efficacious from the standpoint of abolishing pain as the drugs later employed, nevertheless other anesthetics were experimented with in order to obtain a more prolonged action. Experiments on myself led me to believe that nupercaine and Eucupin could fulfill that purpose. While both of the latter drugs are more toxic than procaine, this deficiency is, however, compensated for by the fact that they are effective in very much higher dilutions than procaine, thus making it possible to use much smaller quantities of the crude drug. The ideal anesthetic for this purpose is still to be found, but suitable solutions of nupercaine or Eucupin will, on the average, produce from three to four hours of complete freedom from pain and perhaps an additional hour or two of partial relief. An occasional case may be encountered such as the two in this series, one of which had eight hours and the other six hours of complete absence of pain, but with the drugs employed in this series no more than four hours of complete relief should be expected.

In most instances, a few drops of adrenalin were added to each vial of solution injected with the double purpose of controlling capillary bleeding due to needle puncture

TABLE I. ANESTHETIC AGENTS USED

	CASES
Novocain with adrenalin	7
Novocain without adrenalin	7
1:2,000 nupercaine with adrenalin	9
1:2,000 nupercaine without adrenalin	6
1:1,500 nupercaine with adrenalin	27
1:1,500 nupercaine without adrenalin	2
1:1,000 nupercaine with adrenalin	8
1:1,000 nupercaine without adrenalin	3
Standard Eucupin with adrenalin	12
Standard Eucupin without adrenalin	5
0.5% Eucupin plus 1% procaine and adrenal	13
0.5% Eucupin plus 2% procaine without adrenalin	1

and of delaying absorption of the anesthetic solution. Further studies will be made with a view to determine whether the adrenalin added has any effect on the duration of anesthesia and the length of labor.

Two patients had to be subjected to cesarean section after paracervical injections were made, and fortunately both patients and their babies left the hospital in good condition. Of course in cases where cesarean section is contemplated or likely, paracervical injections should not be performed because of the possibility of contamination and infection. In none of the cases where forceps or other obstetric maneuvers followed paracervical injections were there any complications except in the one case described above where a postpartum chill and fever occurred.

Patients with conditions such as chronic cardiac disease, multiple fibroids, hyperthyroidism, and psychoneurosis were injected without complication and with excellent effect. Absence of anxiety following paracervical injection is striking. This effect would indicate its use in patients who are tense, agitated, or anxious.

Unsolicited comments made by patients varied from "It's wonderful" to "Promise me another delivery like this, Doctor, and I'll have another baby next year."

In the patient who had a postpartum chill, it is of course very possible that the paracervical injection was the etiological factor, but one cannot be certain of that for other competent producing causes existed. She was in active labor for over twenty-four hours on a hot summer day when the outside temperature reached over 100° F. Her membranes were ruptured for almost forty-eight hours and forceps delivery was found necessary. Any of the factors mentioned above beside the paracervical injection could have been responsible for the rise in temperature. She was treated with sulfadiazine and in forty-eight hours the temperature reached normal and remained so far the remainder of her stay in the hospital. She and the baby were discharged in good condition on the ninth postpartum day.

One patient developed marked postpartum distention. Here again, while the anesthetic solution may very well have been the causative factor, there can be no assurance that such was the case. The patient was highly neurotic and agitated. The cervix was rigid, and though a multipara, the labor lasted over thirty-six hours. Delivery was spontaneous. All of us have seen cases of postpartum distention where no form of anesthesia was employed, especially so in tense and anxious patients.

Serious complications may theoretically follow paracervical injection. These would include infection, punctures of the uterus, intestines, blood vessels, and fetal structures. Absolute sterility, extreme care and vigilance are necessary if one is to avoid serious complications and consequences. Whether any punctures took place in this series, I have no way of knowing, but certainly there were no clinical indications of such accidents.

In two instances, a slowing of the fetal heart rate was noted but whether the anesthetic solution was responsible it is impossible to state. Both babies were born alive and although one had erythroblastosis, both left the hospital in good condition.

One infant was stillborn, but in this case it is quite evident that the anesthetic solution had nothing whatever to do with the infant's demise; a very tight cord around the neck had undoubtedly produced asphyxia which was responsible for the death.

Summary

A series of 100 cases in which paracervical anesthesia was employed is described. The indications, the method of injection, the anesthetic agents used, the results, and complications are discussed.

Conclusions

The injection of anesthetic solutions paracervically produces prompt relief from the pain caused by uterine contractions.

It is a simple matter to inject the solutions, and with proper technique and precautions it should prove safe and free from serious complications.

Solutions of procaine, nupercaine, and Eucupin with and without the addition of adrenalin are effective. The relief afforded when these drugs are injected paracervically is much more prompt and pronounced than when drugs are used which act on the central nervous system. Nupercaine and Eucupin induce anesthesia which lasts much longer than that obtained with procaine. Investigations are in progress to find an agent or agents which will secure longer periods of anesthesia with safety.

Uterine contractions are not inhibited and an appreciable percentage of patients deliver spontaneously.

No cases of shock have been encountered nor have any alarming symptoms been noted.

Grateful appreciation is hereby acknowledged to the members of the obstetric nursing staff for their cooperation and interest. I also wish to thank Mr. Leo Reich, our pharmacist, for his collaboration and zeal. My thanks to the Wintthrop Chemical Company for supplying novocain, to Mr. Robert C. Mautner and the Ciba Company for his cheerful cooperation and their supply of nupercaine, and to Dr. John Miskel of the Rare Chemicals Corporation for his valuable aid and suggestions and the supply of Eucupin.

References

1. Gellert, P.: *Monatschr. f. Geburtsh. u. Gynäk.* 73: 143, 1926.
2. Pribram, E.: *Klin. Wehnschr.* 6: 1282, 1927.
3. Henriët, J.: *Strasbourg méd.* 97: 622, 1937.
4. Henriët, J., and Valdejo, A.: *Idem.* 624.
5. Rosenfeld, S. S.: *Am. J. Surg.* 58: 207, 1942.

ON A NONCLOTTING COMPONENT OF POSTPARTUM BLOOD

EMANUEL GREENBERG, M.D., NEW YORK, N. Y.

From the Buffalo General Hospital and the University of Buffalo School of Medicine)

THE flow of blood which issues from the uterus following delivery of the products of conception appears to be divisible into several individual components. A study of the separate clotting characteristics of these components in a series of twenty-five cases reveals that one of these components does not clot. The recognition of this nonclotting component may be of value in the understanding and effective control of postpartum hemorrhage which (since the relative conquest of puerperal infection with sulfonamides and antibiotics) is the greatest cause of maternal mortality today.

Postpartum blood, according to this study, is divisible into three main parts: (1) The blood that flows following delivery of the fetus but before placental separation (probably traumatic cervical and vaginal blood). (2) The flow of blood associated with placental separation. (3) The flow of blood following the delivery of the placenta.

The latter component, which is the nonclotting component, issues from the uterus from the time the placenta is separated up to twenty-four or more hours after delivery. The blood of this third component flows from the uterus either spontaneously, or upon gentle manual transabdominal uterine compression.

Of the 25 cases studied, one was a curetted four-month missed abortion, and one was a cesarean section followed by hysterectomy. The others were normal vaginal deliveries.

Methods

A set of four autoclaved test tubes was placed on every instrument table for each delivery. About 5 c.c. of blood were collected in a test tube at the following times:

1. Following delivery of the fetus but before placental separation (Sample 1).

2. During placental separation (Sample 2).

3. Following delivery of the placenta. This blood was separately collected at intervals of five minutes, ten minutes, one hour, and six hours following delivery of the placenta (Samples 3, 4, 5, 6).

The five- and ten-minute postplacental samples were collected in the delivery room. The one- and six-hour samples were collected in the postpartum room. Antecubital vein clotting times were done in each instance.

In cases where an episiotomy was performed, the sterile collecting test tube was inserted above the episiotomy so as not to include the local traumatic bleeding. No cases of gross cervical lacerations were included in this series.

Results

Sample 1.—This sample consisted of a small amount of blood (5 to 20 c.c.) which probably resulted from uterovaginal tract trauma. Blood which clotted promptly was collected in 15 of the 25 cases. In 6 cases there was no bleeding, and in the first case a sample failed to be collected. In one case, the blood failed to clot. One case was a cesarean section, and one a curettage for a four-month missed abortion. (The sample which did not clot was a more vivid arterial red than the other samples.)

Sample 2.—This sample was collected simultaneously with placental separation. The blood was of a dark venous color and clotted very fast. Its fast clotting time was believed to be owing to the fact that it began to clot retroplacentally while still in the uterus and was practically clotted when it reached the test tube held at the introitus. The blood clotted in 21 cases. Of the remaining 4 cases, in only one case did the blood fail to clot. In one case there was no bleeding; in one case a sample failed to be collected, and one case was a curettage following a four-month missed abortion, where the only samples taken were the one- and six-hour specimens.

Sample 3 (The sample collected five minutes after delivery of the placenta).—This sample did not clot in 17 of the 25 cases. Of these 17 cases, 3 of the test tubes which contained nonclotting blood exhibited a small clot which was believed to be a "contaminant" from blood clots present in the uterus which originated from the placental site. There was no bleeding in one case. The blood clotted in 5 cases (one of these was definitely "contaminated" by traumatic bleeding). One case was a missed abortion where the only samples taken were the one- and six-hour specimens. One case was a cesarean section followed by hysterectomy; the blood expressed from the myometrium did not clot. The blood of Sample 3 was a vivid arterial red as contrasted to the deep venous blue of Sample 2.

Sample 4 (The sample taken ten minutes after delivery of the placenta).—The sample was a vivid arterial red. This sample did not clot in 18 of the 25 cases. Of these 18 cases two were "contaminated" by a small clot discernible at the bottom of the test tube. There was no sample collected in one case, and no bleeding in two cases. Two samples clotted, but one was obviously contaminated by the clotting blood of traumatic bleeding. One case was a curettage of a four-month missed abortion and no samples except the one- and six-hour samples were taken. One case was a cesarean section followed by hysterectomy; blood expressed from the myometrium did not clot.

Sample 5 (The sample taken by slight abdominouterine compression one hour after delivery of the placenta).—Of the 25 cases, one was a cesarean section followed by hysterectomy. The blood clotted in one case. In the remaining 23 cases, including one curettage of a missed abortion, the blood failed to clot (even after days, when the samples could be

agitated and the cells seen to re-enter their original state of suspension). The nonclotting blood was of a vivid arterial red color as opposed to the deep venous blue color of placental separation blood. Of the 23 test tube samples that failed to clot, two contained small "contaminatory" clots.

Sample 6 (This sample taken by slight abdominouterine compression six hours after delivery of the placenta).—Of the 25 cases, one was a cesarean section following hysterectomy. There was no bleeding (no samples obtainable) in three cases. The remaining 21 cases, including one curettage of a missed abortion, showed no clotting and no "contaminatory" clotting even after days.

TABLE I. THE INCIDENCE OF CLOTTING OF THE COMPONENTS OF POSTPARTUM UTERINE BLOOD

PATIENT	SAMPLE 1 FOLLOWING DELIVERY OF BABY BUT BEFORE PLACENTAL SEPARATION	SAMPLE 2 FIRST BLOOD OF PLACENTAL SEPARATION	SAMPLE 3 FIVE MINUTES AFTER DELIVERY OF PLACENTA	SAMPLE 4 TEN MINUTES AFTER DELIVERY OF PLACENTA	SAMPLE 5 ONE HOUR AFTER DELIVERY OF PLACENTA	SAMPLE 6 SIX HOURS AFTER DELIVERY OF PLACENTA	SAMPLE 7 ANTE- CUBITAL CLOTTING TIME (MIN.)
1. M. R. 357661	No sample collected	No sample collected	No clotting	No clotting	No clotting	No bleeding	3½
2. L. B. 357686	Clotted	Clotted	No clotting	No clotting	No clotting	No clotting	3½
3. A. F. 357802	Clotted	Clotted	No clotting	No clotting	No clotting	No bleeding	1½
4. D. G. 357854	Clotted	Clotted	No clotting	No clotting (See note)	No clotting	No clotting	2
5. H. B. 357909	No bleeding	Clotted	No clotting	No clotting	No clotting	No clotting	2½
6. V. C. 357964	No bleeding	Clotted	No clotting	No clotting	No clotting	No clotting	5½
7. S. A. 357987	No bleeding	Clotted	No bleeding	No bleeding	No clotting (See note)	No clotting	3
8. H. K. 358024	No bleeding	No bleeding	No clotting (See note)	No clotting (See note)	No clotting	No clotting	4
9. T. C. 358184	D & C following 4-month missed abortion No samples taken except one- and six-hour				No clotting	No bleeding	4½
10. B. H. 358416	Clotted	Clotted	No clotting	No bleeding	No clotting	No clotting	1½
11. V. G. 358225	No clotting	Clotted	No clotting	No sample collected	No clotting	No clotting	3
12. E. R. 358295	Clotted	Clotted	Clotted	Clotted	No clotting	No clotting	1½
13. M. H. 358344	Clotted	Clotted	No clotting	No clotting	No clotting	No clotting	½
14. E. K. 358364	Clotted	Clotted	No clotting	No clotting	No clotting	No clotting	1½
15. S. S. 358371	Clotted	Clotted	(Contaminated by trauma)		No clotting	No clotting	1½
16. M. K. 358417	Clotted	Clotted	Clotted No clotting	Clotted No clotting	No clotting	No clotting	8
17. G. C. 358474	Cesarean sec- tion fol- lowed by hysterectomy	Clotted	Blood expressed myometrium did not clot	from did not	Cesarean section fol- lowed by hysterectomy		1½
18. C. P. 358483	Clotted	Clotted	No clotting	No clotting	No clotting	No clotting	2
19. C. F. 358482	Clotted	Clotted	No clotting (See note)	No clotting	No clotting	No clotting	1½
20. A. M. 358444	Clotted	Clotted	Clotted	No clotting	No clotting	No clotting	6
21. C. B. 358523	Clotted	Clotted	No clotting (See note)	No clotting	Clotted	No clotting	3½
22. D. K. 358578	No bleeding	No clotting	No clotting	No clotting	No clotting (See note)	No clotting	2
23. E. D. 358545	Clotted	Clotted	Clotted	No clotting	No clotting (See note)	No clotting	3
24. D. H. 358599	No bleeding	Clotted	No clotting	No clotting	No clotting	No clotting	4
25. M. L. 358567	Clotted	Clotted	Clotted	No clotting	No clotting	No clotting	1½

These tubes of nonclotting blood contained a few small clots from trauma or placental site bleeding.

Conclusions

1. Postpartum uterine blood is separable into several components. The three chief components are the uterine blood samples collectable (a) before, (b) during, and (c) after placental separation.

2. One of the components of postpartum blood does not clot. This is the component that flows from the uterus after delivery of the placenta.

3. The nonclotting component of postpartum blood is, together with atonicity of the uterus, directly concerned with the normal postpartum blood loss, and may be directly related to the unsolved problem of pathologic and too often fatal postpartum hemorrhage.

4. Correlations of this study with past clinical observations in postpartum hemorrhage are now in progress by the author and soon will be described.

1141 PARK AVENUE

PRIMARY OVARIAN PREGNANCY*

JAMES F. NORTON, M.D., AND NICHOLAS M. ALTER, M.D., JERSEY CITY, N. J.

(From the Margaret Hague Maternity Hospital)

BECAUSE of the relative infrequency of primary ovarian pregnancy, the accompanying case report which seems quite accurately to fit the necessary criteria for the establishment of this pathologic diagnosis is thought to be of sufficient interest to warrant presentation.

S. M. (History No. 56376) was admitted to the hospital on Feb. 12, 1944. She was 35 years old, gravida viii, para ii, and had had two previous uneventful pregnancies and labors. Her last menstrual period was Sept. 18, 1943, giving her an expected date of confinement of June 25, 1944. Her menstrual periods began at the age of 14 years, recurred every twenty-eight days, and were two or three days in duration; she says she was always very regular.

In 1927 she had a normal spontaneous delivery at home after a forty-eight-hour labor, and in 1935 a second normal spontaneous home delivery after a twelve-hour labor.

She had a long, somewhat complicated, but relatively important, past surgical history. In October, 1930, after having had an episode of vaginal bleeding for two and one-half months (the last five weeks of which the bleeding was estimated as severe), she was operated on in a hospital in a neighboring community, and a right salpingectomy and appendicectomy was carried out. The reported pathologic findings were as follows: "The right tube was markedly enlarged and adherent to the right ovary. The mass was friable and easily separated from the right ovary. The tube was thickened near the uterine end. The tube near the fimbria was enlarged to the size of an egg. No ulcerated areas noted. Appendix was long but did not appear inflamed. Postoperative diagnosis—old ectopic gestation right; pathologic hematocele; old ectopic cannot be ruled out." She made an uneventful recovery and was discharged in late September, 1930.

Three years later, in August, 1933, she was readmitted to the same hospital complaining that since the time of her original operation in 1930 she had been unable to become pregnant. Her menstrual periods in the interim had been regular. Diagnosis on discharge was "Cystic left ovary. Tubo-ovarian disease." The treatment consisted of rest and sterile douches, and after two weeks of hospitalization she was discharged improved.

*Presented at a meeting of the New York Obstetrical Society, Feb. 13, 1945.

Her next readmittance to this same neighboring hospital was Nov. 21, 1943 (which was about two months after her last menstrual period of Sept. 18, 1943). She remained in the hospital for six days, having received symptomatic treatment for what was diagnosed as "Pregnancy, angulation of ureter."

About three months following this, Feb. 12, 1944, her first admission to the Margaret Hague Maternity Hospital took place. At this time she complained of pain in the lower half of her abdomen and the passing for the past few days of clots about the size of a fifty-cent piece, and an amenorrhea going back to Sept. 18, 1943 (about four and one-half months).

General physical examination revealed nothing untoward. Examination of the abdomen disclosed a midline suprapubic scar extending from the symphysis to within 2.5 to 3 cm. of the umbilicus, and an irregular midline suprapubic mass extending about 12 cm. above the symphysis pubis. On vaginal examination the cervix uteri was found directed upward under the symphysis, and a little to the right of the midline. A somewhat tender mass about 12 by 12 cm. in diameter was felt a little to the left of the midline, and a small nontender mass about 3 by 5 cm. a little to the right. The impression was a threatened abortion of an intrauterine pregnancy in a fibroid uterus.

On May 9, 1944, because there had been no increase in the size of the uterus and because she herself said that she had passed no formed elements through the vagina, she was readmitted to the hospital for further investigation. A Friedman test at this time was negative, and flat plates of the abdomen showed fetal parts whose estimated age was 12 to 16 weeks. The suprapubic enlargement previously referred to still measured about 10 cm. After a stay of about ten days, she was discharged with a change in diagnosis to a missed abortion in a fibroid uterus. She was given instructions to return in the event of any inordinate vaginal bleeding and was further instructed as to what she might expect in the event of the completion of the abortion. She at this time would not entertain any thought of interference because she had some hopes that her pregnancy might still go on.

She was not seen again until about five months later, when on Oct. 9, 1944, she returned to the hospital, saying that she had passed no masses of any kind, that her abdomen had not increased in size, and that she wanted now to be operated on. It was learned that she had some vaginal bleeding at more or less irregular intervals since the time of her last discharge in May. The examination was essentially the same at the time of her last discharge, except perhaps for a slight diminution in the size of her suprapubic enlargement. X-rays still showed a fetus which the roentgenologist estimated to be about 16 weeks of age. On the following day, Oct. 10, 1944, laparotomy was carried out with a preoperative diagnosis of a missed abortion of sixteen weeks' gestation which had existed for about fifty-six weeks.

On opening the abdomen through a midline incision, a large mass measuring about 15 by 12 by 12 cm. presented below the incision and was distinctly a little to the left of the midline and occupying the position of the left ovary. Coursing over the top of the tumor mass was the thinned out and attenuated left tube; the tube and mass were attached to the small nonpregnant uterus, which was pushed a little to the right. The peritoneal surface of the uterus and the surface of the mass and also the pelvic peritoneum in general were studded with small firm endometrial transplants. The right tube was markedly dilated and contained a hydrosalpinx of about 2.5 cm. in diameter and was closely adherent to the right ovary. The mass, which now quite definitely was identified as ovarian in origin, was for the most part intraligamentous and was removed much after the fashion of a large ovarian cyst, without any technical difficulty.

During the operative procedure a chocolate brown-colored fluid escaped from the lowermost part of the mass, and in its cystlike cavity could be palpated the small dead fetus previously identified by x-ray. The completion of the operation was uneventful and the hydrosalpinx was removed. Postoperative course was uncomplicated and she was discharged from the hospital well on the fourteenth postoperative day.

The findings at the time of operation have definitely satisfied the first three of the accepted postulates. The establishment of the fourth, that is, the presence of ovarian tissue in the sac, is due to Dr. Nicholas M. Alter, the pathologist at the hospital.

Pathologic Description.—Gross: There is an irregular oval-shaped mass which weighs 390 grams; it measures 15 by 10 by 10 cm. On one side, there is a sac which resembles ovarian tissue with very numerous follicles; it has whitish smooth capsule; through an opening a macerated fetus is seen lying in the sac (about four months). Behind the sac there is a great deal of hemorrhagic fibrinous material.

Microscopic: Section shows fibrous tissue. At one side some suggestion of decidual reaction is seen. Microscopic sections were taken of all parts, but only the sac containing

the fetus showed organized tissue. The inner lining of the sac shows homogeneous pink-stained tissue of necrotic material around which there is only a suggestion of decidual cells; then follows a layer of hyalinized tissue, behind which a fibrous wall is seen with few lymphocytes. One section shows an old hyalinized corpus luteum, which is surrounded by typical ovarian stroma of small dark spindle cells. No ovogenesis is noted. Some rather fresh hemorrhage is seen in the outer layer. Section of the hemorrhagic mass around the ovary shows only layers of old fibrinous material without any cellular element.

Microscopic Diagnosis: Ovarian pregnancy.

58 KENSINGTON AVENUE.

Discussion

NICHOLAS M. ALTER (by invitation).—The specimen received weighed 390 grams; it consists of an ovarian mass with tube attached; tube is 6 cm. in length, has free fimbriated end; serosa is smooth; lumen is narrow throughout; wall thin. The ovarian mass consists essentially of two parts (Fig. 1); the upper portion is an enlarged cystic ovary that measures 15 by 10 by 10 cm.; surface shows typical white covering with very numerous follicular cysts measuring from 3 to 8 mm. in diameter; attached to the ovary at the base there is a hemorrhagic mass which, on cross section particularly, shows definite layering of old and more recent hemorrhages. On opening ovary, there is a cystic cavity from which some very thick chocolate-like material is exuding. Ovary forms a sac with wall not exceeding 10 mm. in thickness anywhere. The cavity itself is filled by a mummified fetus (Fig. 2) approximately 16 cm. in length; it shows only dried bones and skin; it is in an advanced state of absorption; the umbilical cord is attached to the upper portion of the hemorrhagic mass, which is rather gray and firmer where the cord is attached; then layers of fibrinous material are seen which are covered by softer hemorrhagic surface.

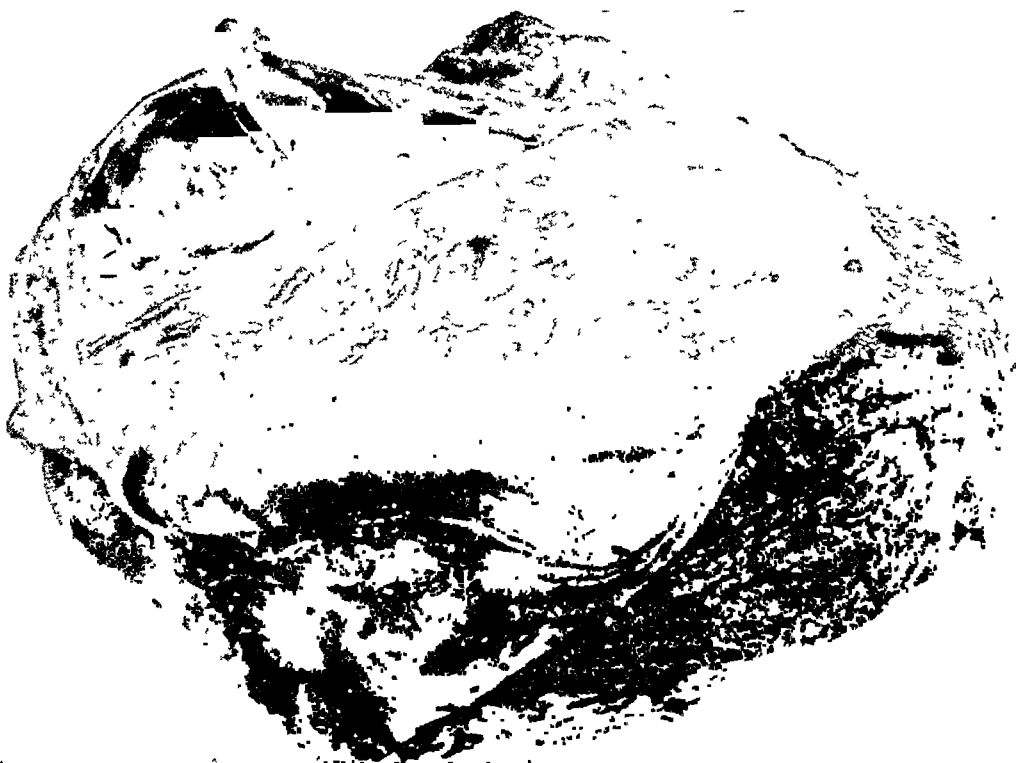


Fig. 1.—Ovarian sac with fetus through opening. Ovarian surface with follicular cysts. Subplacental hemorrhage that extended into broad ligament.

Microscopic sections were made in a series over the entire ovarian capsule and base. Sections show uniformly a lining which is distinctly amniotic in nature with fairly well-preserved cells; beneath this there are layers of large pale cells, which are in various degrees of regression and cannot be definitely identified as decidual and lutein (Fig. 3). Beyond this ovarian stroma is present, in some sections containing corpus albicans or some follicular cysts. Ovogenesis has not been observed in any of the sections. Sections at the base show only outlines of the chorionic villi, so-called "shadows" embedded in old fibrinous material.



Fig. 2.—Mummified fetus in ovarian sac. Cross section of placenta with layered hemorrhages.



Fig. 3.—Photomicrograph of ovarian sac wall showing amniotic lining with subsequent decidual-lutein tissue, adjacent ovarian stroma with corpus luteum ($\times 37$).

In the case reported the gross and microscopic evidence meets the requirements of intra-follicular or primary ovarian pregnancy.

The fetus reached the unusual age of about 4 months without rupture of the ovarian sac, but with subplacental dissection into the broad ligament.

After gestation stopped, the clinical and pathologic picture was that of missed abortion of unknown length of time.

ARRHENOBLASTOMA*

DEWITT C. DAUGHTRY, M.D., RICHMOND, VA.

THE rarity of this tumor and its most interesting features seem to warrant the reporting of this case.

Case Report

A married Negro nullipara, 37 years of age, came to the Duluth Clinic complaining of pain in the right lower abdomen. The pain was of a dull, aching, persistent character and associated with some nausea and vomiting and had its onset ten days previously. A hurried physical examination revealed an exquisitely tender mass in the right tubo-ovarian region, and a tentative diagnosis of right tubo-ovarian abscess was made. The patient remained in the hospital five days, at which time all symptoms had disappeared, but the pelvic mass persisted. The patient was discharged with a diagnosis of subsiding right tubo-ovarian abscess.

Three weeks later the patient returned to the hospital with essentially the same complaints. She stated that she was symptom-free for one week after leaving the hospital but symptoms recurred when she returned to work. At this time a careful history was obtained and it was essentially as follows: Onset of menses at 12 years of age. Periods recurred at 28-day intervals and flowed normally for four days. No change from the normal was noted until ten years ago, at the age of twenty-seven years, at which time her periods became irregular and were accompanied by dysmenorrhea and menorrhagia. During the year to follow, her periods became more irregular and ceased completely nine years ago, at the age of 28 years. Her only explanation was witchcraft. With cessation of menses, mild menopausal symptoms appeared. These consisted of vertigo, warm sensations, and marked nervousness. She had been married since 17 years of age; her husband was living and well. She had had no pregnancies and she denied the use of contraceptives. Two or three years ago she began to notice an increase in growth of hair over the entire body. The growth of hair on the face became so noticeable that she started shaving a year ago. The facial hair gradually increased in growth until she was shaving three or four times a week. There was no appreciable change in weight, nor decrease in libido. She had noticed no change in her voice.

Physical examination revealed a thin, Negro woman of stated age, measuring 5 feet 6 inches in height and weighing 113 pounds. The voice seemed rather husky for a woman. The contour and musculature of the body appeared masculine in character. There was a masculine type of hirsutism over the entire body. The facial hair had the appearance of a two days' growth of beard on the average adult male. Ophthalmoscopic examination was negative. Chest appeared rather muscular. There was marked atrophy of breast with no palpable masses. A few long coarse hairs were noted about the areolae and over the sternum. Her blood pressure was 120/80. Abdomen was scaphoid with slight muscular resistance and some tenderness over the right lower quadrant. The pelvis was anthropoid in type and there was pronounced masculine distribution of pubic hair. Labia majora were atrophic, exaggerating the appearance of the markedly hypertrophied clitoris. Her clitoris measured $1\frac{1}{2}$ inches in length and resembled the penis of a child. There was a well-formed prepuce and glans. In the right lower quadrant was palpated a lemon-sized, firm, freely movable, and slightly tender mass. The left ovary was thought to be slightly enlarged but was not tender. The vaginal rugae were atrophic and a mucopurulent discharge was present. No lymphadenopathy was noted.

Laboratory Findings.—Red blood cell count was 4,150,000; hemoglobin 80 per cent; white blood cell count was 5,200; differential count revealed 64 per cent polymorphonuclear leucocytes and 36 per cent lymphocytes. The Kline and Wassermann tests were negative. Urine was reported as negative. Her basal metabolic rate was +5 and the Friedman test was negative.

X-ray examination showed the sella to be normal in size with no evidence of bony erosion. There was no evidence of body demineralization and no evidence of metastasis to bones of the pelvis, chest, or skull. X-ray of the chest was negative. Pyelograms revealed normal left kidney, with the right kidney ectopic and lying at the brim of the pelvis.

*Presented before the Staff of the Duluth Clinic, Duluth, Minn., March 1, 1943.

At operation the right ovary was represented by an ovoid firm tumor mass measuring 7 cm. in diameter. There were no adhesions and it was in normal relationship to the other pelvic structures. The left ovary was cystic and the uterus was studded with numerous subserous fibroids. A supracervical hysterectomy and bilateral salpingo-oophorectomy were performed. The abdomen was explored for metastasis but no evidence of such was found. The right kidney was ectopic and located at the brim of the pelvis in close proximity to the appendix.

Pathologic specimen was an ovoid, smooth, firm, and solid mass measuring 7 cm. in diameter. On sectioning, the tumor appeared distinctly yellow and its surface was granular and hard, due to diffuse calcification of the central portion. Microscopic examination revealed rather small basophilic spindle-shaped cells without apparent intercellular stroma. Nuclei were quite uniform as to size and staining intensity. In one portion of the tumor fairly typical tubular structures were seen. Mitotic figures were rare, indicating a very low grade of malignancy. There were many patchy areas of hyaline degeneration and in some of these areas calcium deposition had taken place, thus denoting a tumor of long standing. The neoplasm occupied the central portion of the ovary and was an expansive-type growth with a fairly normal thin zone of ovarian tissue between the tunica and the neoplastic center (Fig. 1). The opposite ovary was normal except for many cystic follicles.

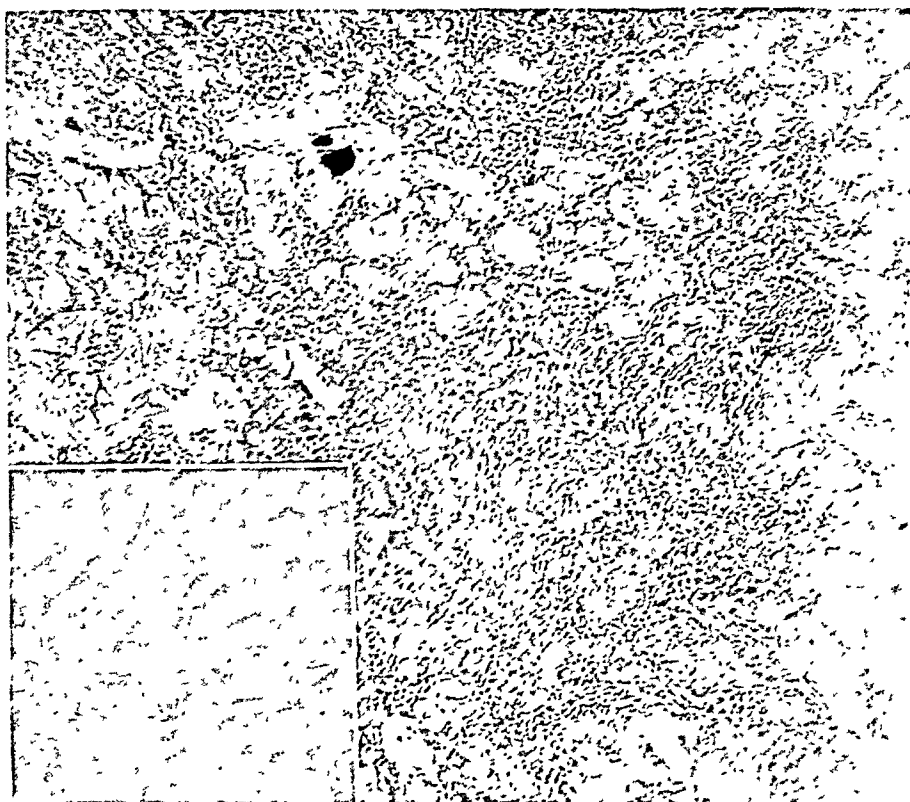


Fig. 1.—Low-power view revealing patchy irregularly shaped areas of moderate cellularity, separated by moderately abundant, frequently hyalinized stroma with occasional small areas of calcium deposits. Inset is a selected area of more cellular nature with mesothelium-like cells with oval or elongated nuclei and thin cytoplasm.

The postoperative course was uneventful and the patient was discharged from the hospital on the fifteenth day.

The subsequent course has been very interesting. The masculine appearance has decreased considerably. The clitoris is softer and much smaller. Facial hair is now scant and silky. The patient gained 5 pounds the first two months following operation. Her mental attitude has greatly improved. There has been no evidence of metastasis.

Discussion and Differential Diagnosis

Cardinal findings in this case were a history of normal maturity, followed by sterility, amenorrhea, masculine hirsutism and general appearance, husky voice, atrophic breasts, anthropoid pelvis, atrophy of labia majora, pelvic tumor, hypertrophy of clitoris, and no change in weight nor decrease in libido.

Whenever a case presents the above findings, one should always consider arrhenoblastoma in the differential diagnosis. In making the final diagnosis, several conditions producing a similar clinical picture were considered and excluded. Those considered were: thymic tumors, basophilic adenoma of the pituitary gland, and adrenal cortex tumors. An "oat-cell" thymic tumor may produce a confusing picture. It is a very rare tumor and was excluded by means of a negative x-ray of the chest.

Basophilic adenoma of the pituitary received very little consideration in the differential diagnosis. In only one reported case has the diagnosis of basophilic adenoma masked the true diagnosis. It was excluded because there was no bony erosion of the sella, no obesity, no bony demineralization, no hypertension, no glycosuria, marked hypertrophy of the clitoris, excessive hirsutism with virilism, husky voice, clear skin, and a palpable pelvic tumor.

Tumor of the adrenal cortex was more difficult to eliminate. This is far more common than arrhenoblastoma and produces a very similar clinical picture. The cardinal findings are: sterility, obesity, amenorrhea, excessive masculine hirsutism particularly on the chin, husky voice, atrophic breasts, and pronounced enlargement of the clitoris. Acne and hypertension are common findings. Due to the pressure of the tumor upon the kidney pelvis, an abnormal pyelogram further substantiates the diagnosis. It was likewise excluded with some degree of certainty, and the final diagnosis of arrhenoblastoma of the ovary was reached.

In reviewing the literature it is interesting to note that most, if not all, of the few reported cases have been diagnosed postoperatively. This is due, at least in part, to poor history taking. In fact this case was mistakenly diagnosed on a previous admission because a thorough history was not taken and the patient's general appearance must have been ignored.

Summary and Conclusions

1. Another case of arrhenoblastoma is presented. A preoperative diagnosis was made chiefly because a more careful history was taken and a more thorough physical examination made.

2. Findings in this case were: sterility, amenorrhea, no appreciable change in weight, clear skin, masculine hirsutism and body contour, husky voice, normal blood pressure, hypertrophy of clitoris, atrophy of breasts and labia majora, pelvic tumor, no decrease in libido, normal basal metabolic rate, and essentially negative x-rays.

3. The case was treated by simple surgical excision, with marked decrease of masculine features in a period of six months.

The author is deeply indebted to Dr. Arthur H. Wells, of Duluth, Minnesota, for assistance in the preparation of this paper.

EDEMA OF THE UVULA AND EDEMA OF THE GLOTTIS—A REACTION TO DEMEROL-SCOPOLAMINE ANALGESIA

MURRAY STEINBERG, M.D., BALTIMORE, MD.

(From the Department of Obstetrics, Sinai Hospital of Baltimore)

EDEMA of the uvula and edema of the glottis complicating demerol-scopolamine analgesia have not been reported hitherto. It may prove an extremely serious condition. A review of the literature of the past ten years revealed only one reference to "swelling" of the uvula to "five or six times its normal size,"¹ as a reaction to scopolamine. Schumann,² in a review of 1,000 cases of demerol-scopolamine analgesia in labor, makes no reference to this complication.

From November, 1944, until March 1, 1945, demerol and scopolamine analgesia was used routinely during the labor of all clinic patients and most private patients at the Sinai Hospital of Baltimore, a total of approximately 400 cases. The routine adopted was essentially that used by Schumann,² at the Boston Lying-In Hospital. The orders were posted as follows:

Routine Medication: (All intramuscularly)

Initial Medication:

Demerol, 100 mg.	} when patient began to complain; in primiparas usually about 3 cm., and in multiparas with the onset of regular pains.
Scopolamine, $\frac{1}{400}$ grain	

Subsequent Medication:

Demerol, 100 mg.—repeated every three hours.

Scopolamine, $\frac{1}{150}$ grain— $\frac{3}{4}$ hour after initial dose.

Scopolamine, $\frac{1}{200}$ grain—two hours after initial dose.

Scopolamine, $\frac{1}{200}$ grain—every two hours thereafter until patient is ready to deliver.

Case Reports

CASE 1.—A. S. (History No. U-34897), a 37-year-old white primipara who had been widowed during the second month of pregnancy, was first seen by her obstetrician on Oct. 27, 1944, when approximately five months pregnant: Patient's menses had always been irregular and she did not remember the date of her last period. The estimated date of confinement, calculated from the onset of fetal movements and the size of uterus, was approximately Feb. 15, 1945. Past medical and surgical history was negative. There was no history of allergy. Patient's prenatal course was uneventful. Approximately three weeks prior to term, since the vertex was still floating, x-ray pelvimetry was performed in order to rule out contraction of pelvis. A slightly contracted pelvis was reported with the obstetric conjugate 10.7 cm., and the transverse of the inlet 11.7 cm.

At 8:15 P.M. on Feb. 14, 1945, her membranes ruptured spontaneously. She arrived at the hospital one hour later, reporting mild, irregular pains. Examination at this time revealed the presenting part to be three fingerbreadths above the ischial spine, the presentation left occiput transverse, with the cervix undilated. Later that evening, the patient's pains became stronger and more frequent. At 12:25 A.M. on February 15, cervix was 1 cm. dilated. By 1:15 A.M., patient was complaining of severe pain and demerol-scopolamine analgesia was ordered according to the routine described above. Eight hours later, patient had progressed to 7 cm. with the presenting part at the level of the spine. In the next six hours, despite good pain and stimulation with pitocin, patient did not make any progress. During the entire period, the fetal heart was good. At 7:00 P.M., patient's temperature had risen to 100° F. (rectally) (98.6° F. [orally] on admission), and pulse to 134. Because of the fear of intra-partum infection, sulfadiazine and penicillin therapy were instituted. At 9:30 P.M. on February 15, a cesarean section was decided upon.

At about this time, the nurse reported that the patient was having difficulty with breathing and was complaining of "something in her throat." The patient appeared cyanotic, breathing with difficulty, and frantically pointing to her throat. Examination of pharynx

revealed a red, edematous uvula, enlarged eight to ten times its normal size, practically completely obstructing the respiratory passage. A laryngologist was called and he scarified the uvula with multiple vertical incisions. Under this therapy, the patient's symptoms were greatly relieved and the uvula shrank down to two to three times its normal size in fifteen to twenty minutes.

At 12:30 A.M. on February 16, under cyclopropane-oxygen-ether anesthesia, a low cervical cesarean section was performed and an 8-pound 4-ounce living female infant was delivered.

Patient was returned to her room at approximately 1:45 A.M. At this time, she again began to breathe with difficulty and again became cyanotic. Examination of the pharynx revealed the uvula had again enlarged to approximately eight times its normal size. Three minims of adrenalin subcutaneously failed to have any effect. Scarification was again performed, relieving the patient to a great degree, but not completely. At 2:30 A.M., patient again became extremely dyspneic and cyanotic. Examination of the pharynx revealed the uvula to be normal in size. The otolaryngological consultant was called, who, after examination, diagnosed edema of the glottis. Bronchoscopy was attempted but it was not possible to pass the bronchoscope because of the extreme edema. As a last measure, tracheotomy was performed, relieving the patient immensely.

Postoperatively, the patient did extremely well except for a mild endometritis. Tracheotomy tube was removed on the fourth postoperative and the patient discharged on the nineteenth postoperative day.

This patient had received one $\frac{1}{100}$ -grain, one $\frac{1}{150}$ -grain, ten $\frac{1}{200}$ -grain doses of scopolamine, and seven 100-mg. doses of demerol in twenty hours, according to the routine aforementioned. Skin test for scopolamine sensitivity was positive—3 plus according to scales used by Kirschbaum.¹



Fig. 1.—L. M. (History No. U-33204). Edematous uvula following demerol-scopolamine analgesia. Photograph taken just prior to scarification.

CASE 2.—L. M. (History No. U-33204), a 21-year-old white primipara, was first seen at the Sinai Hospital Obstetric Dispensary on Sept. 29, 1944. At that time, she was approximately 26 weeks pregnant. Last menstrual period occurred on April 21, 1944. Estimated date of confinement, Jan. 28, 1945. Family history negative. Past medical and surgical history entirely negative. Prenatal course uneventful. On Feb. 13, 1945, examination revealed a term-sized baby, cephalic presentation, head unengaged. X-ray pelvimetry was ordered, revealing an average-sized gynecoid-type pelvis.

At 11:45 P.M. on February 27, patient was admitted to the labor room with ruptured membranes present for two and one-half hours, pains occurring every five minutes. Examination revealed a cephalic presentation with the presenting part 3 fingerbreadths above the ischial spines, cervix soft, 1 fingertip dilated. At 1:00 A.M., February 28, demerol-scopolamine analgesia was begun according to routine. After 100 mg. of demerol and $\frac{1}{100}$ grain of scopolamine, sedation was discontinued inasmuch as the uterine contractions became weaker and patient failed to progress. At 10 A.M., examination revealed the cervix to be 4 cm.

dilated, the presenting part at the level of the spine, strong uterine contractions occurring every three to four minutes. Sedation was resumed. At 1:45 P.M., cervix was fully dilated and the presenting part 2 fingerbreadths below the ischial spine. In total, the patient had received two 100-mg. doses of demerol, two $\frac{1}{100}$ -grain, one $\frac{1}{150}$ -grain, and one $\frac{1}{200}$ -grain doses of scopolamine within eleven hours. Skin tests for scopolamine sensitivity gave a 1 plus positive reaction.

A full-term, living male child was delivered as a left occiput anterior by low forceps and left medial lateral episiotomy at 1:55 P.M., under local infiltration and pudendal block anesthesia, using 1 per cent procaine hydrochloride.

At 2:55 P.M., patient was returned to her room. At 3:15 P.M., the nurse reported that the patient was coughing, dyspneic, and moderately cyanotic. Examination of the pharynx revealed a red, edematous uvula, enlarged to about eight times its normal size. Scarification followed by argyrol swabs relieved this condition.

Postpartum course was uneventful.

CASE 3.—M. C. (History No. U-29213-2), a 30-year-old white primipara, was first seen by her obstetrician on July 24, 1944. At that time, she was approximately ten weeks pregnant. Last menstrual period, May 5, 1944. Estimated date of confinement, Feb. 12, 1945. Family history, past medical and surgical history, entirely negative, except for a laparotomy for an ectopic pregnancy in November, 1943.

At 3:00 A.M. on Feb. 19, 1945, patient was admitted to the labor room with pains occurring every six to seven minutes, cervix soft, 1 fingerbreadth dilated, cephalic presentation with presenting part 2 fingerbreadths above the spines. At 5:30 A.M., demerol-scopolamine analgesia was ordered. The patient received 100 mg. of demerol, one $\frac{1}{100}$ -grain, and one $\frac{1}{150}$ -grain dose of scopolamine by 6:15 A.M. Sedation was then discontinued and resumed again at 12:30 P.M., at which time the patient was 4 to 5 cm. dilated. By 2:30 P.M., patient had received another 100-mg. dose of demerol, one $\frac{1}{100}$ -grain, one $\frac{1}{150}$ -grain and one $\frac{1}{200}$ -grain dose of scopolamine. Sedation again was discontinued inasmuch as uterine contractions were becoming weaker and progress was slow. At 6:30 P.M., another 100 mg. dose of demerol and one $\frac{1}{100}$ -grain dose of scopolamine were given. One $\frac{1}{150}$ -grain dose of scopolamine was repeated at 7:15 P.M. In total, the patient had received three 100-mg. doses of demerol, three $\frac{1}{100}$ -grain, three $\frac{1}{150}$ -grain, and one $\frac{1}{200}$ grain doses of scopolamine within thirteen hours and forty-five minutes. Cervix was fully dilated at 9:20 P.M., the head at the level of the ischial spine, position right occiput transverse. With the aid of pitocin stimulation, rotation occurred spontaneously to right occiput anterior, and presenting part descended to three fingerbreadths below the ischial spines. A full-term, living female infant was delivered by low forceps and midline episiotomy at 11:24 P.M. under gas-oxygen-ether anesthesia.

The patient was returned to her room at 12:30 A.M. on February 20. At 9:00 A.M., patient complained of a sore throat and constant impulse to cough. Examination of the pharynx revealed a red edematous uvula enlarged to three or four times its normal size. Under the influence of repeated argyrol swabs, the uvula was reduced to normal size within two days. Scarification was not necessary. Skin test for scopolamine sensitivity gave a 2 to 3 plus positive reaction.

Postpartum course was otherwise uneventful except for pyelitis responding to sulfadiazine therapy.

Comment

Three cases of edema of the uvula, one with edema of the glottis as well, have been described. Careful questioning of these patients revealed no similar reaction occurring previously nor any history of allergy or allergic reactions. While in labor, these patients were on a liquid diet, consisting of tea, coffee, and fruit juices. The only medication received during labor was demerol, scopolamine, and pitocin and Klotogen (vitamin K preparation). One of these patients (A. S. History No. U-34897) developed edema of the uvula prior to delivery, and edema of the uvula and glottis following delivery by cesarean section. The other two patients developed edema of the uvula following delivery. L. M. (History No. U-33204) received 1 c.c. of ergotrate and 1 c.c. of pitocin intravenously with delivery of the anterior shoulder. M. C. (History No. U-29213-2) received 1 c.c. of ergotrate intravenously with delivery of the anterior shoulder. A. S. (History No. U-34897) received 1 c.c. of ergotrate and 1 c.c. of pitocin intravenously during cesarean section. One patient, M. C. (History No. U-29213-2), was receiving routine postpartum medication consisting of

ergotrate, aspirin, codeine, seconal, and ferrous sulfate, when the reaction developed. The only common denominator of significance in these three cases was demerol-scopolamine analgesia. Edema of the uvula and edema of the glottis have not been reported as a reaction to demerol, but Kirschbaum¹ has stated that, as a reaction to scopolamine, "the uvula may swell to five or six times its normal size and may appear markedly reddened. The redness may persist for several days. Argyrol swabs or throat irrigations will correct the condition." After a review of these three cases and in view of the afore-mentioned report, we feel that we can ascribe this reaction to scopolamine.* However, we have not ruled out the possibility that this peculiar reaction was due to the combined effect of demerol and scopolamine. It is to be noted that all these patients had received scopolamine over a long period of time (eleven to twenty hours) and in large total dosage (0.0216 to 0.055 grain).

It appears strange that others have not observed this reaction. It will be noted that A. S. retched several times during her labor. Since this is so common an occurrence, we did not pay particular attention to her or to any of our other patients with the same complaint. Perhaps this desire to retch in many other cases is due to irritation of the pharynx by a minor degree of edema of the uvula. Careful observation will determine the answer to this question.

Nowhere have we found any report of edema of the glottis as a reaction to scopolamine analgesia. In view of the uvular edema, however, we believe the same etiologic agent responsible for edema of the glottis. The anesthetist and the medical consultants do not believe it was due to the anesthesia since one case began before the cyclopropane-oxygen-ether anesthesia, one followed nitrous oxide-oxygen-ether, and the other followed pudendal block with procaine.

These three patients all exhibited positive skin tests for sensitivity to scopolamine. Many of our patients, however, who exhibited no reaction to scopolamine analgesia, reacted with positive skin tests for scopolamine sensitivity. As a result, we do not believe too much faith can be placed on this skin test as an indication that such a reaction will develop.

In view of the gravity of the reaction and its serious implications, we have discontinued routine demerol-scopolamine analgesia on the Obstetrical Service at the Sinai Hospital of Baltimore.

Acknowledgments are made to Dr. William B. Schapiro and Dr. Raymond Goldberg for their aid in the preparation of this paper.

References

1. Kirschbaum, H. M.: *AM. J. OBST. & GYNEC.* 44: 664, 1942.
2. Schumann, W. R.: *AM. J. OBST. & GYNEC.* 47: 93, 1944.

Addendum

Since the original manuscript has been submitted for publication, an additional case of edema of the uvula has occurred on the Obstetric Service of Sinai Hospital. This reaction followed seconal-scopolamine analgesia in contrast to the original three cases reported where the reaction occurred following demerol-scopolamine analgesia. As a result, we are more firmly convinced that this particular reaction is due to the scopolamine and not to the demerol or combination of demerol and scopolamine. The case history is as follows:

G. S. (U-36175-1), a 26-year-old white primipara, was admitted in active labor on May 20, 1945. When she had progressed to 4 cm. dilatation, strong uterine contractions occurring every three minutes, sedation with 3 grains of seconal and $\frac{1}{400}$ grain of scopolamine was instituted, and $\frac{1}{150}$ grain of scopolamine was repeated in forty-five minutes. Two hours and forty-five minutes later, a full-term, living male child was delivered under gas-oxygen-ether anesthesia. Approximately two hours later, the patient began to complain of a "lump in the back of the throat" and she began to cough violently. Examination of the pharynx at this time revealed a red, edematous uvula, about four to five times its normal size. It must be noted that examination of the pharynx two hours prior to delivery revealed a normal-sized uvula. Argyrol therapy was instituted (as previously described) and in approximately eighteen hours the uvula returned to its normal size.

*Assay of the tablets (hyoscine hydrobromide, $\frac{1}{100}$ grain) by the Analytical Control Laboratory of Sharp & Dohme reveals "the tablets are well within the N.F. standard of 88-112% and vary only a slight amount from the original assay conducted at the time of manufacture, namely, September 1940."

PHANTOM LIMB SYNDROME COMPLICATING PREGNANCY AND PUERPERIUM

GEORGE A. WILLIAMS, M.D., ATLANTA, GA.

(From the Emily Winship Woodruff Maternity Center of the Crawford W. Long Hospital)

THE phantom limb syndrome, one of the most distressing of the sequelae of amputations of the extremities, has received renewed attention recently. The subject has been reviewed thoroughly by White¹ who summarized clearly the accepted facts as to its etiology and treatment. In its most serious form the sensations of motion in the amputated extremity are accompanied by painful spasms or twitchings in the stump itself. The mechanism involved presumably is stimulation of the afferent fibers of the sectioned nerves, sometimes by a definite neuroma, but the occasional persistence of painful sensations after repeated reamputation, peripheral neurectomy, posterior rhizotomy and even cordotomy suggests that cortical sensory projection may occur. The present case is reported because it was a most distressing complication of an otherwise normal pregnancy and puerperium.

Mrs. R. G. F., aged 30 years, white, married, gravida ii, para i, had sustained a right mid-thigh amputation in 1931 because of crushing trauma in a railroad accident. She accepted her disability philosophically and appeared to be well adjusted psychologically. She learned to use her prosthesis well, married, and successfully carried on the dual career of homemaker and businesswoman. Her stump gave little trouble other than occasional mildly annoying sensations of motion in the lost ankle and foot. Her first pregnancy, labor, and puerperium in 1938 were said to have been normal. In 1943 she was referred by her internist because of backache. Possible factors were obesity, postural disturbance resulting from the amputation and retroversion-flexion of the uterus. Pessary treatment of the latter gave no relief. Orthopedic consultation gave no additional information, but a corset proved to be of some value.

The last menses occurred Feb. 20, 1944, and when examined at the end of the first trimester the enlarged uterus was still retroverted and retroflexed so it was again replaced on a pessary for six weeks. General health, blood pressure, blood count, and urinalysis were normal, and the Kahn test was negative. In spite of the increasing weight there was little of the awkwardness of pregnancy, the patient continued to use her prosthesis well, and the course of gestation was normal until the fifth calendar month.

On Aug. 7, 1944, the patient began to experience painful sensations of motion in the amputated ankle and foot and painful clonic movements of the stump itself. Bed rest in the home, salicylates, pentobarbital sodium, hypodermic injections of morphine, and, after nausea developed, paraldehyde by rectum, all were used without benefit over a period of three days while a hospitalization crisis made it impossible to secure a bed. Her condition steadily worsened and when finally admitted to the hospital on August 9, the vicious triad of pain, fatigue, and dehydration were all too apparent. The patient constantly moaned and tossed in bed as the violent clonic spasms of the stump occurred every two to three minutes. In spite of the decreased leverage of the muscles it was virtually impossible to restrain the violent contractions which were largely in the flexors and adductors. When the patient attempted to lie prone the entire trunk was lifted and twisted by them. In addition, there were violent voluntary expulsive efforts as if the patient were in the second stage of labor, and she seemed just as unable to refrain from them. However, there was at no time any evidence of uterine contractions, descent of the presenting part, or parturitional changes in the cervix. The blood pressure was 120/70, oral temperature 99° F., pulse 100, and respirations 20.

In neurologic consultation, Dr. William A. Smith advised temporary interruption of the painful impulses, so a trial of continuous caudal anesthesia was begun. Using metycaine, 1.5 per cent, after the method of Hingson, little technical difficulty was experienced notwithstanding the obesity and the constant movement of the patient. Anesthesia appeared promptly and was gradually increased until with a dose of 60 c.c. it reached to level of the eighth

thoracic nerves bilaterally. The muscles of the perineum and left lower extremity became flaccid but the effect on the bladder was contrary to the usual experience. There was an immediate forceful voiding in bed and the patient remained incontinent for sixteen hours. The effects of the anesthetic on the amputation stump were puzzling. Complete skin anesthesia developed and the patient was relieved of all pain and the voluntary expulsive efforts ceased. The muscles of the stump became flaccid except that the clonic spasms of the adductors continued but in markedly decreased frequency and amplitude. The anesthesia was purposely allowed to wear off at the end of sixty-five minutes, after which the original picture returned except for the expulsive efforts which never recurred. A second injection of the same dose of metycaine solution gave results which closely paralleled the first, and after its action terminated, the pain, spasms, etc., again returned to their original severity.

On the following day Dr. Charles Ward was asked to try blocking off the right lumbar sympathetic ganglia with procaine solution. This was followed by almost the identical picture of relief from pain and decrease in frequency and amplitude of the spasms of the stump as followed caudal anesthesia. These all returned when the effect of the injection wore off, however. After that Dr. Ward blocked the femoral and obturator nerve trunks with procaine solution and virtually the same temporary results were obtained. On the next day he diffusely infiltrated the "trigger areas" of the stump itself with procaine, 1 per cent, with dramatic results. The patient was not only permanently relieved of all pain except some residual soreness of the abdomen and thigh stump, but the spasmodic contractions ceased and did not return after the anesthesia wore off. The patient rapidly improved and was transferred home on the fifth hospital day.

The course of pregnancy continued uneventfully except for a mild urinary tract infection in the sixth month. On Dec. 6, 1944, labor was induced because of albuminuria and rising blood pressure. The patient was delivered of a normal male infant after a labor of seven hours. The response of the pains of labor to analgesics was striking when compared to the failure of such drugs to relieve the phantom limb pain. Demerol, 100 mg., and scopolamine, 0.5 mg., intramuscularly, gave perfect amnesia and analgesia for three hours, the patient sleeping soundly between the contractions and making no outcry with them.

The puerperium was uneventful until painful contractions of the amputation stump began again on the fourth day. Morphine and pentobarbital sodium again failed to give relief, so Dr. Ward repeated his infiltration of the "trigger areas" in the stump with procaine, with prompt and satisfactory results. The contractions did not cease immediately this time but continued painlessly for several days. The patient was discharged from the hospital on the sixth puerperal day. On her final postpartum visit at six weeks she was about as comfortable as usual.

No definite conclusions can be drawn from a single case of phantom limb syndrome such as the one herein described, but it is presented merely as data on a distressing complication of pregnancy and the puerperium which may become more common as women are increasingly exposed to the hazards of industry, traffic, and warfare.

Reference

1. White, James C.: J. A. M. A. 124: 1030, 1944.

384 PEACHTREE STREET, N. E.

ERYTHROBLASTOSIS FETALIS IN TWIN PREGNANCY

MONRAD E. AABERG, M.D., AND CHARLES ROBY, PH.D., BOSTON, MASS.

(From the Boston Lying-in Hospital and the Department of Obstetrics of Harvard University Medical School)

IN VIEW of recent reports on the etiology of erythroblastosis fetal, it was felt that a presentation of a case of twin pregnancy exhibiting two varieties of erythroblastosis would be of interest.

Case Report

Past Obstetric History.—Mrs. M. C., a primipara, was delivered in 1937 by low forceps of a 6-pound 12-ounce normal infant. (Unfortunately, the child died in an automobile accident nine months later.) The patient was in the hospital for nine weeks before delivery with bilateral pyelitis. During this hospitalization she received one blood transfusion because of secondary anemia. The donor was the patient's husband. There was only a slight reaction.

In 1939, as a para ii, the patient was delivered normally of a 7-pound 4-ounce infant which lived five hours. The baby was diagnosed clinically as erythroblastosis fetal, hydrops variety, because of an enlarged liver and spleen and some edema. No autopsy was performed, but the placenta was typical, on microscopic section, of a mild hydrops variety of erythroblastosis fetal. The blood picture of the infant showed a hemoglobin of 25 per cent; a red blood cell count of 1,480,000; a white blood cell count of 28,000. There were 42 erythroblasts for every 100 white blood cells counted. During this pregnancy the patient was hospitalized for seven weeks before delivery because of severe pyelitis, and received three blood transfusions for secondary anemia. After the third transfusion (husband's blood) the patient experienced a chill, and the temperature rose to 107.4° F. There was a short interval of coma.

Present Pregnancy.—The patient, now 26 years old, para iii, was due, Dec. 12, 1941. She was admitted to the hospital on Oct. 17, 1941, because of albuminuria of ten days' duration and a slight pitting edema of the legs and ankles.

Physical examination revealed a patient who was quite thin and pale, not in labor. There was moderate dilatation of the veins over the upper abdomen. The fundus was at the xiphoid. The uterus by palpation was much larger than dates would indicate. Previous roentgenogram indicated twin pregnancy. One fetal heart was 160 per minute in the left lower quadrant; the other, 144 in the upper left quadrant. The extremities showed pitting edema up to the knees. Rectal examination revealed the cervix to be soft, partly taken up, and a finger tip dilated. One fetal head could be felt in the pelvis.

Diagnosis.—Para iii, thirty-three weeks pregnant by dates with twin pregnancy, with chronic pyelonephritis, mild pre-eclampsia, and suspected erythroblastotic infant (at least one twin).

Laboratory Data.—The patient was found to be Rh negative, group A; the husband Rh positive, group O. They were not related.

Urine examination showed a moderate amount of albumin and occasional red and white blood cells. There were a few coarse granular casts and a few bacteria. Blood examination showed a hemoglobin of 60 per cent by Sahli; white blood count, 7,000; red blood count, 3,660,000; nonprotein nitrogen, 43 mg. per cent; total proteins, 5.12 mg. per cent; fibrinogen, 0.51 mg. per cent; serum albumin, 2.65 mg. per cent; serum globulin, 1.96 mg. per cent.

Labor and Delivery.—On October 18, the patient went into spontaneous labor at 7:30 P.M. Three and one-half hours later, she was delivered normally, by the vertex, of Twin 1, a female weighing 4 pounds, 8 ounces. The patient did not receive analgesia or anesthesia. The baby cried immediately after birth and seemed to be in fairly good condition except for its moderate pallor. Vaginal examination revealed Twin 2 also presenting by the vertex which had marked pitting edema of the scalp. A stillborn male infant, weighing 6 pounds, 6½ ounces, was delivered by low forceps under intravenous pentothal sodium anesthesia. The infant showed massive generalized edema, characteristic of the hydrops variety of erythroblastosis fetal.

Rh Factor Studies.—Cord blood was taken for the purpose of determining the presence of the Rh factor. Both twins were found to be Rh positive and Group O. The mother's blood showed a low titer for anti-Rh agglutinins. There was no titer two weeks later.

Infant Blood Studies.—Immediate blood counts were made on the surviving twin. The hemoglobin was 50 per cent (Sahli); the red cell count, 1,180,000; the white cell count, 30,000. The corrected white cell count was 23,850. There were 380 nucleated red blood cells for every 100 white cells counted. There were 9.4 per cent reticulocytes.

Transfusion.—Ten hours following delivery the surviving infant was moderately jaundiced. By this time an Rh-negative donor was obtained and the baby was transfused with 50 c.c. of citrated blood. The hemoglobin rose to 60 per cent and the infant's condition seemed quite satisfactory. Twenty-six hours later the jaundice had increased and the hemoglobin had dropped to 42 per cent. Preparations were made for a second transfusion when the infant became cyanotic and succumbed.

Placentas.—Examination of the placentas showed them to be double ovum and partially fused. Together they weighed 1,900 grams. One placenta was extremely large and the other small.

The larger placenta measured 24 by 22 by 2.5 to 3.5 cm., and was partially circumvallate. The cord was swollen and edematous. The fetal surface was blue-gray, slightly granular, and glistening. The maternal surface was pale, boggy, soft, deeply fissured, with large friable swollen cotyledons.

The smaller placenta measured 16 by 16 by 2 cm., and, likewise, was partially circumvallate. The maternal surface was uniform, pinkish gray, and somewhat paler than usual; the fetal surface was not remarkable.

Impression.—Double-ovum partially fused twin placentas, each partially circumvallate. Microscopically, the placenta of Twin 1 showed the vessels to be peripherally placed and small, containing many nucleated red blood cells. The placenta of Twin 2 showed the pathognomonic findings of the hydrops variety of erythroblastosis. The villi were large, and the stroma was edematous. The vessels contained many nucleated red cells.

Twin 1. Autopsy Findings.—Although complete autopsies were performed on these twins, only the spleen and liver examination are reported here. The body was that of a female premature infant, weighing 1,880 grams and measuring 42 cm. in length.

Spleen: Grossly, the spleen was dark purple in color and weighed 26 grams (normal full-term weight 8 grams). Microscopically, there were many large, dark brown, pigment-containing monocytes. There was considerable hematopoietic activity, especially of the red blood cell series.

Liver: Grossly, the liver had a uniform reddish brown color with some petechial hemorrhage beneath its capsule. It weighed 114 grams (normal full-term weight 78 grams). Microscopically, there was extensive hematopoiesis. Many nucleated red cells were contained in the sinusoids. Almost all the canaliculi and many of the ducts were plugged with bile.

Twin 2. Autopsy Findings.—The body was that of a well-developed, markedly edematous male infant, measuring 42 cm. in length and weighing 2,825 grams. There was a marked pitting edema of the entire skin.

Spleen: Grossly, the spleen was dark purple in color and weighed 28 grams. Microscopically, there were many nucleated red blood cells in the sinusoids as well as many foci of hematopoiesis.

Liver: Grossly, the liver was pale brown in color and weighed 110 grams. Microscopically, the liver cells contained considerable golden brown pigment. There was extensive hematopoietic activity with as many as 4 or 5 foci per lobule and occasionally as many as 10 to 15 cells per focus. Many nucleated red cells were present.

Diagnosis.—1. Prematurity. 2. Erythroblastosis fetalis (hydrops type).

Comment

Landsteiner and Weiner¹ demonstrated the occurrence of a new antigen in the human erythrocytes which they termed the Rh factor. When a woman who does not have the Rh factor in her red blood cells (Rh negative) carries a fetus which does have the Rh factor (Rh positive), iso-immunization takes place. The Rh factor is known to be inherited as a Mendelian dominant gene. Not all children born of an Rh-negative woman impregnated by an Rh-positive man will show evidence of erythroblastosis fetalis.

This case illustrates the possible iso-immunization of the mother by the fetal red blood cells. In response to this immunization the mother produces

agglutinins (anti-Rh) which pass through the placenta and destroy the fetal red blood cells, producing erythroblastosis fetalis.²

In this case, an antepartum diagnosis of erythroblastosis fetalis was made on at least one of the twins on the basis of: (1) the past obstetric history, (2) the Rh status of the husband and wife, (3) the history of blood transfusion reactions. The homozygous or heterozygous status of the husband was not determined, but in all probability he was homozygous since three out of four infants showed evidence of erythroblastosis fetalis.

The principal aim in presenting this case is its demonstration of the occurrence of two varieties of erythroblastosis fetalis in a twin pregnancy. It is interesting from the standpoint of heredity that the male infant exhibited the more severe form of erythroblastosis (hydrops), while the female demonstrated the less severe type (icterus gravis). A search of the literature fails to reveal any similar cases.^{3, 4}

Addendum

Fifteen months later, in January, 1943, this patient again registered for prenatal care. Her last menstrual period was Nov. 5, 1942. The patient's blood at ten and one-half weeks' gestation, showed the presence of anti-Rh agglutinins. In view of the previous history of three erythroblastotic infants, blood transfusion reactions, chronic pyelonephritis, pre-eclampsia, and the presence of anti-Rh agglutinins, it was decided that a therapeutic interruption should be done. Therefore an abdominal hysterotomy and bilateral Irving sterilization were performed.

Microscopic examination of the placenta showed evidence of hydropic changes. It is evident that had the patient been permitted to continue her pregnancy, she undoubtedly would have delivered another erythroblastotic hydropic infant.

References

1. Landsteiner, K., and Weiner, A. S.: J. Exper. Med. 74: 309, 1941.
2. Levine, Philip, et al.: AM. J. OBST. & GYN. 42: 925, 1941.
3. DeLange, C.: Acta paediat. 13: 292, 1932.
4. Macklin, M.: Am. J. Dis. Child. 53: 1245, 1937.

221 LONGWOOD AVENUE

PREGNANCY COMPLICATED BY A SUBDURAL BRAIN ABSCESS*

MAX SCHNEIDER, M.D., NEW YORK, N. Y.

(From the Sydenham Hospital)

D. J., a 23-year-old Negro woman, was admitted to Sydenham Hospital as an emergency case on Nov. 18, 1943, when she was seven and one-half months pregnant. The complaints for which she was admitted had begun three days previously and consisted of headache, vomiting, an abscess in the roof of her mouth, chills and fever, and recurring attacks of sharp abdominal pain lasting from two to three minutes.

The previous history was interesting. Since the age of 9 years, she had had eighteen operations for osteomyelitis in various parts of her body. She had given birth to two children at other hospitals. In 1941 her first child was delivered by low forceps without any complications. One year later, a cesarean section was done for her second child. The hospital report of this delivery reads as follows:

"Patient was admitted in active labor. The physical examination revealed (1) a fractured femur, (2) separation of symphysis, (3) congenital dislocation of hip, and (4) widespread osteomyelitic lesions. The head was not engaged. A cesarean section was done, and there was an uneventful recovery."

*Presented Dec. 11, 1944, at a meeting of the Sydenham Hospital Clinical Society.

D. J., had an unusual social history which may have had some bearing on her symptomatology. Her parents were dead and she was living with an older sister. The latter had prevented her from marrying the man who was the father of her first two children and responsible for this pregnancy.

The physical examination showed a short statured, undernourished Negro woman who walked with a marked limp. The eyes were clear, no icterus present. The left side of the face was swollen and edematous. There was marked tenderness over the left maxillary bone and upper gums. On the hard palate on the left side there was a localized, fluctuating swelling. Dental caries was present, and the upper left gum was edematous. The heart and lungs did not show any abnormalities.

The abdominal examination revealed: (1) a seven and one-half months' pregnancy, with normal fetal heart sounds, (2) lower midline operative scar, (3) open sinus exuding a serous discharge in left inguinal region, (4) liver felt 2 fingers and spleen 1 finger below the costal margins. Scattered over the trunk and the extremities were eighteen scars of previous incisions for the recurrent attacks of osteomyelitis.

The temperature on admission was 102° F.; pulse 120; respirations 24; blood pressure 90/60; hemoglobin 56 per cent; red blood count 3,240,000; white blood count 8,800, with 36 per cent staff forms. The urine contained a very heavy trace of albumin and 2 plus acetone.

A roentgenogram of the skull showed cloudiness on the left frontal, anterior ethmoidal, and sphenoidal sinuses. No other abnormalities were noted.

After admission, the patient was seen immediately by the attending physician on the Nose and Throat Service and by the dentist. They both diagnosed a palatal abscess caused by an osteomyelitic process. Operation was not deemed necessary and the patient was to receive general supportive treatment.

Two days after admission, the palatal abscess ruptured spontaneously. The temperature dropped to normal within forty-eight hours and the swelling and edema of the face and gums gradually subsided. Within a week, the mouth condition was apparently completely cured.

The vomiting and headache continued and the patient developed an acetoneuria. On December 7 (nineteen days after admission), the urine showed albumin 2 plus; acetone 2 plus; diacetic acid 2 plus. The carbon dioxide combining power was 47 volumes per cent. The blood pressure was 90/60; hemoglobin 50 per cent; temperature 99.4° F.

It was found that the patient had a bilateral papilledema and hemorrhages in the eye grounds. Because we believed she might have a possible toxemia of pregnancy, she was transferred to the obstetric service. There, to combat the acetoneuria and dehydration, she was given intravenous infusions of 5 per cent glucose in normal saline, and to combat the headache she received codeine and aspirin suppositories. Vitamin B complex and 100 mg. of ascorbic acid were given in daily intramuscular injections.

Not convinced that the patient had a toxemia of pregnancy, a neurological opinion was requested and obtained on December 10, as follows:

"Fundi show bilateral papilledema. Left pupil greater than right, but right pupil reacts better to light. No paresis of eyeballs. No facial weakness. Tuning fork test heard better on right. To pinprick, there is diminution of second and fifth nerves (in second branch). Deep reflexes obtained and equal. No neck rigidity. No Kernig. Vibration intact. Finger-nose test shows no true ataxia. *Opinion:* Although a toxemia is to be considered, the patient probably has an extension of the infection in her left upper jaw, into the base of the skull."

A lumbar puncture on the following day showed clear fluid under normal pressure with negative laboratory findings. A roentgenogram of the base of the skull was negative.

Ophthalmologic examination revealed that "both discs are swollen in nasal part. Retinal veins much dilated and engorged. On right disc there is a fresh hemorrhage. In the lower half of the macular region there are extensive glistening, yellowish patches, evidently very superficially located. *Diagnosis:* neuroretinitis exudativa."

On the twenty-third hospital day, the following opinion was recorded: "Fundi show a definite papilledema with hemorrhages, engorgement of veins, and a suggestion of compressions of veins by arteries. The spinal fluid is essentially normal. The question to be decided here is whether one is dealing with some form of toxemia of pregnancy or some intracranial lesion which is responsible for the symptoms and neuroretinopathy. Since it is difficult, if not impossible, to make a definite decision in this regard at this particular time, it would seem wise to follow a conservative course and to continue the administration of glucose or saline, and to keep the patient under a longer period of observation. Blood chemistry should be repeated. Particular attention should be paid to any signs pointing to a focal brain lesion.

In spite of the negative spinal fluid findings, when one sizes up the case as a whole, the suspicion of intracranial pathology appears warranted. Certainly it is not a meningitis; but the possibility of a brain abscess cannot as yet be excluded. There is not enough in the clinical picture to favor a diagnosis of toxemia of pregnancy."

The patient was kept under close observation for another three weeks. At one time there was marked tenderness over the left side of the base of the skull; the ophthalmologist found a diplopia, which lasted for about one week.

A psychiatric study showed effects of a bad life situation.

A careful record was made of the patient's fluid and food intake. Several series of intravenous infusions of 5 per cent glucose in normal saline were given whenever the urine showed the presence of acetone.

The patient's condition improved steadily. The headaches diminished in frequency and intensity; the vomiting stopped. The eye ground examination showed a gradual disappearance of choked discs. The blood pressure remained low. After the first forty-eight hours, the temperature was never higher than 99.4° F., but the sedimentation rate was rather high—41 mm. in one hour. The hemoglobin, however, dropped to 48 per cent.

The medical consultants advised waiting for further localization of a possible cerebral lesion; the neurologist, on the other hand, thought the pregnancy should be terminated so that it would be easier to treat a possible brain lesion if this became necessary.

On December 28, a neurosurgeon saw the case and expressed the following opinion: "The differential diagnosis lies between toxemia of pregnancy and brain abscess, metastatic, secondary to an osteomyelitis. To me it seems more like a brain abscess. Its localization cannot be determined, as there are no localizing signs. It would be best to terminate this pregnancy *now* as the patient is in excellent condition, and she will be better prepared for surgery of a brain lesion, with the baby removed. Sulfadiazine should be started. Electroencephalography might be of value."

The patient, now thirty-eight weeks pregnant, was given a transfusion of 500 c.c. of whole blood on the day prior to operation.

Operation.—On December 31 (her forty-third hospital day), a low flap cesarean section was done. The incision in the skin was made under 1 per cent novocain local anesthesia, but a general anesthesia had to be given before the peritoneal cavity was opened. The operation was uncomplicated, with a minimal loss of blood. A live baby, weighing five pounds, was extracted. A Madlener sterilization was also done.

During the operation the anesthetist noticed the sudden appearance of a profuse purulent discharge from the left ear. A few hours later an otological examination showed no apparent tenderness over the left mastoid. The profuse discharge did not allow of inspection of the drum. It was believed that the patient may have had an osteomyelitis of the temporo-sphenoidal bone or petrous portion which discharged through the ear.

It was the neurosurgeon's opinion that the patient had had an osteomyelitis of the base of the skull, on the left side, with the formation of an extradural abscess. This had finally burrowed its way through the outside at the external auditory meatus.

On the second postoperative day, the patient's temperature rose to 103° F. but dropped to normal within forty-eight hours. She received another blood transfusion and chemotherapy for five days. The wound healed by primary union. The ear discharge stopped in a few days.

The patient was discharged on the fourteenth postoperative day, free of all symptoms. She was seen six months later in the follow-up clinic. She had gained considerable weight and was quite happy.

Summary

A seven and one-half months pregnant Negro woman, 23 years of age, was admitted to the hospital complaining of headache, vomiting, chills, fever, and an abscess on the roof of her mouth. The abscess was actually a recurrent attack of osteomyelitis similar to attacks that she had been having for the past eighteen years. It ruptured spontaneously, but headache and vomiting persisted. Papilledema was found in the eye grounds. Acetonuria developed.

The question of toxemia of pregnancy arose. The blood pressure, however, always remained low.

The patient was treated symptomatically, with gradual improvement of the symptoms and disappearance of the papilledema.

When the patient was thirty-eight weeks pregnant, a cesarean section was done (repeat cesarean). During the operation, there occurred a sudden profuse discharge of pus from the left ear. This established the diagnosis of subdural brain abscess, which had caused the symptoms simulating a toxemia of pregnancy.

Recovery was uneventful.

I herewith wish to express my thanks for the numerous consultations on this case to Drs. Emanuel Appelbaum, Judah Ebin, Hyman H. Osserman, Ernst Waldstein, and Fritz Wengraf.

MYXOSARCOMA OF VAGINA ASSOCIATED WITH EARLY PREGNANCY

FRANK G. S. CHRISTIE, M.D., B.Sc.(MED.) SARNIA, ONTARIO

SARCOMA of the vagina is an exceedingly rare disease. As reported by Tracy,¹ McFarland in 1911 could collect only 101 cases which, with one added, made a total of 102 cases to that date. He stated there were only 68 cases of sarcoma of the vagina (not including sarcoma botryoides) reported in forty-two years. Williams tabulated a consecutive series of 9,226 tumors found in women, of which 2,648 were of uterine origin, and only 54 tumors arose from the vagina. Of the 54 vaginal neoplasms, only two were sarcomas. McFarland's figures revealed that the tumors are found most frequently in the first, second, fourth, and sixth decades of life, with the largest percentage in the fourth decade. The tumor may develop in any part of the vagina but is usually located in the lower portion of the canal.

Case Report

The patient, a married woman of 39 years, was first seen by me April 16, 1940, because of amenorrhea since Jan. 26, 1940. Believing herself to be pregnant for the second time (previous pregnancy twenty years ago), she was reporting for prenatal care. At this time bimanual examination revealed a two- to two-and-one-half-month intrauterine pregnancy, and on the posterior vaginal wall a small, sessile, papillomatous tumor, measuring 2 by 1 cm., located approximately 2 inches from the posterior commissure. It was firm, rather reddened, and bled upon handling. A diagnosis was made of papilloma of vagina complicating early pregnancy. The patient was advised to submit to excision of the tumor for pathologic study. This was done and the tissue report from the Institute of Public Health, University of Western Ontario, London, Canada, is as follows:

Macroscopic Description.—Specimen consists of a small mass of tissue measuring 1.8 by 1.3 by 1 cm. The external surface is fairly smooth as if it had shelled out of a capsule quite readily. It is moderately firm and rubbery in consistency. On section its surface is uniformly grayish in color and rather fibrous in nature.

Microscopic Description.—The pathologic condition is myxosarcoma. Sections of this tissue show it to be partially covered by stratified squamous epithelium. Beneath the epithelial layer the tissue is composed of connective tissue in which a nonencapsulated, moderately cellular tumor nodule is noted. The cells are invading the tissue in a malignant manner. The cells are spherical and ovoid in shape and are supported by a loose myxomatous type of stroma.

After consultation, it was agreed that the uterus should be emptied immediately and radiation therapy instituted. On May 6, 1940, dilatation of the cervix and evacuation of the products of conception were performed. The patient was then referred to Dr. T. Leucutia, Harper Hospital, Detroit, Michigan, under whose direction radiation therapy was carried out as follows:

From May 13 to 18, 1940, supervoltage roentgen therapy was administered in an ambulatory manner. Five portals of entry were used for the purpose of cross-firing the pelvis, one

portal being treated daily. The total dose amounted to 130 per cent S U D at the site of the lesion and 80 per cent S U D on the surface of each portal. The quality of the roentgen rays employed was that obtained with 500 kv., 7 mm. copper. On May 21, patient was admitted to Harper Hospital and 75 mg. of radium in suitable containers (1 mm. Al, 1 mm. brass) were inserted intravaginally into the posterior cervix, as well as the uterine canal, and left in situ for seventy-two hours (5,400 mg. hours).

Roentgen examination of the chest on May 24, 1940, failed to reveal any indication of metastatic disease.



Fig. 1.—Low-power photomicrograph of vaginal wall revealing invasion of sarcomatous cells ($\times 120$).

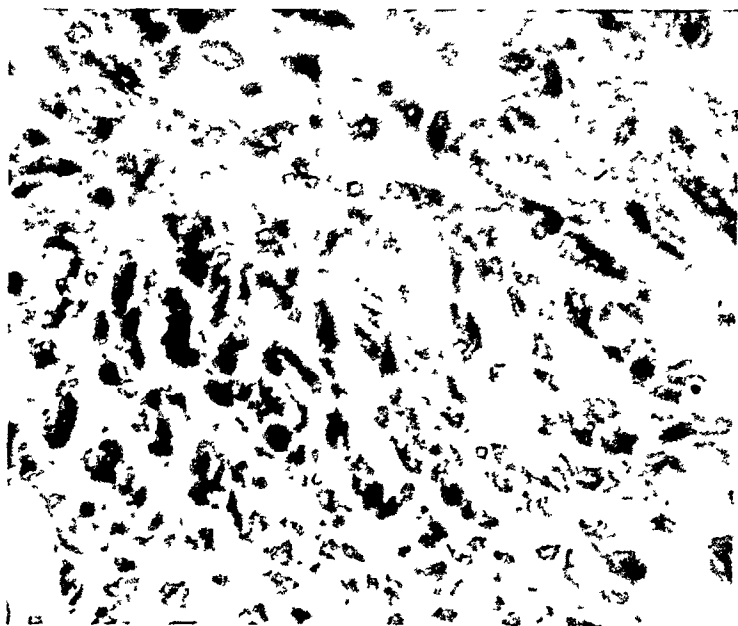


Fig. 2—High-power photomicrograph of sarcomatous field as observed in Fig. 1 ($\times 450$).

The patient was seen at monthly intervals for three months and apart from a moderate proctitis and vaginitis (postradiation) no untoward condition occurred.

A second course of radiation was administered from Aug. 19 to 27, 1940. Again a combination of supervoltage roentgen therapy and intracavitary radium was used. The same technical procedure was applied except for the fact that the radium dosage was reduced to 3,300 mg. hours.

This case was followed for two years at three- to four-month intervals and for the past two years examined every six months. The last pelvic examination was made Oct. 19, 1944 (four and one-half years after the original discovery), and the internal and external genitalia, although quite atrophic, were healthy. A marked stenosis of the rectum has been present almost since the first radiation treatment was given. Her general health is excellent.

At the time of writing, practically five years have elapsed since therapy was instituted, and a reasonably hopeful prognosis now seems quite justified.

Reference

1. Tracy, Stephen E.: *AM. J. OBST. & GYN.* 19: 279, 1930.
178 GEORGE STREET

DOUBLE UTERUS, CERVIX, AND VAGINA WITH PREGNANCY CARRIED TO TERM

EDGAR E. SCHMITZ, M.D., ST. LOUIS, MO.

THIS rather rare anomaly, together with a pregnancy carried to term, warrants reporting, so that the scant accumulated knowledge on the subject may be augmented by the experience gained in the successful termination of this case.

No one sees enough of such deviations from the normal to formulate an opinion as to their treatment, gained solely from firsthand knowledge. It would seem well, therefore, to record experience and procedure here to help round out the picture.

Mrs. X, aged 21 years, came to me in the third month of her pregnancy, totally unaware of any anomalous condition of her genital organs. Her general health had been good and her sexual relations normal in every way. Her only complaint was missed menstruation, which she rightly attributed to a pregnancy.

Examination showed a tall, slender girl, well formed and symmetrically developed. Breasts and external genitals were normal in every detail. Inspection of the vaginal introitus showed a firm rather thick band of tissue which divided the vaginal space into two distinct cylinders of slightly different calibers. The right side being the larger readily admitted a speculum, while the smaller left side took the speculum only with considerable manipulation. There was no connecting aperture anywhere in this septum.

At the top of each of these vaginal canals was a very small but perfectly formed cervix, a miniature, but not infantile, replica of the normal picture. Superimposed on the right cervix was a definitely pregnant uterus, corresponding in size to about the third month of gestation. Continuous with the left cervix was a firm structure about the size and shape of a normal uterine fundus, but lying transversely across the pelvis, forming almost a right angle with the pregnant uterus. Both bodies were separated in their lower segments by an appreciable gap.

As there had been no symptoms of any kind referable to this undoubtedly serious malformation, the situation was explained to both husband and wife, and a period of watchful waiting entered upon. When gestation had proceeded to about four and a half months, it was no longer possible to palpate the nonpregnant uterus on the left side, as it was obscured by the advancing pregnancy.

This brings up a serious point in procedure. Had the patient first presented herself for examination at this stage of her pregnancy, the transverse position of the second uterus would not have been ascertained. One might then have sought guidance from the textbooks and reasoned that a trial of labor would be indicated, surely a most unfortunate decision to be reached in a case of this kind. Knowing, however, that the second uterine body would enter the pelvis in front of an advancing fetal head, no such thought could be here entertained, and delivery by section was advised.

The pregnancy progressed normally in every way. No bleeding, no excessive premature contractions, no metabolic disturbances were noted at any time. Fifteen days prior to the expected date of delivery a section was performed and the following conditions noted:

The pregnant fundus was moderately asymmetrical with a bulging toward the upper left pole and a flattening of the entire mesial side. An incision was made in what appeared to be the proper location, and a viable, normal female infant, weighing 6 pounds, was extracted. The placenta came away easily and the uterine wound was ready for closure. This proved not as easy as at first anticipated, as the flattened mesial fundal wall proved to be very thin indeed. Even in its contracted state it was little thicker than heavy cardboard, while the right side showed the usual tissue depth.

The uterine wall being closed, it was now possible to inspect the pelvis in detail. Following the mesial border of the incised uterus downward, one came to a shallow depression at the level of the cervix, and proceeding laterally to the left, encountered the second uterine body lying transversely in the pelvis. This had the appearance of a normal fundus as to size and consistency, but had only one round ligament and only one tube and ovary, which arose in proper position in the left upper cornu. The right side of this uterus was also slightly flattened and showed no appendages. The fundus which had contained the child also had only one tube and ovary and one round ligament. These arose from the right upper margin and were normal. There were no adnexa on the left side of this organ.

With the uterine musculature thinned out to so disquieting a degree, a condition that could not be discovered except by direct observation, and with a second uterine body blocking the pelvis, which could only be palpated early in pregnancy, a complete and accurate diagnosis is impossible. Confronted with the ever-present danger of hemorrhage or uterine rupture, it would seem that operation is indicated under all conditions.

501 METROPOLITAN BUILDING.

UTERUS DIDELPHYS COMPLICATING PREGNANCY

IRWIN T. CRAIG, LT. COMDR., MEDICAL CORPS, USNR, AND
K. W. SCHENK, LT. COMDR., MEDICAL CORPS, USNR, FORT LAUDERDALE, FLA.

(From the Out-Patient Department, U. S. Naval Air Station)

A CASE of pregnancy in uterus didelphys with small myomas in the nongravid uterus, delivered by cesarean section, is presented herewith.

Mrs. W. P., aged 26 years, gravida i, para 0, was first seen in the outpatient department, June 10, 1944. Her last period was April 13, 1944, and she had slight nausea with occasional vomiting as her chief complaint. Her past history was negative for all diseases except measles, chickenpox, and mumps. She had never had any operations. Menstrual history showed menarche at 12 years of age, and periods had been uninterrupted until her present pregnancy. The interval has been 30 to 32 days, with a heavy six-day flow. There has been no intermenstrual bleeding, and dysmenorrhea has never caused the patient concern.

Physical examination revealed a well-developed, well-nourished white woman, weighing 127 pounds. Blood pressure, 96/70. Urine showed a trace of albumin. Hemoglobin, 79 per cent; red blood cells, 4,460,000; Kahn test, negative.

On pelvic examination a vaginal septum was found extending the full length of the vagina, dividing this structure into two halves. The right half admitted two fingers easily and the left half admitted two fingers with difficulty, indicating that coitus had been practiced chiefly, if not entirely, on the right side of the septum.

Speculum examination revealed two normal-sized cervices, one in each vaginal canal, and there was no attachment of the septum to either cervix. Two separate fundi were identified on bimanual examination, with the right fundus about twice the size of the one on the left. It was felt that we were dealing with a case of pregnancy in the right side of a uterus didelphys.

The course of pregnancy was uneventful except for a *Trichomonas vaginalis* vaginitis which was found in the last month of pregnancy and was untreated at that time. X-ray of the abdomen on Jan. 13, 1945, showed a full-term fetus in a right sacroanterior position with the breech not engaged.

Onset of labor, January 28, was marked by the spontaneous rupture of the membranes with irregular contractions beginning shortly thereafter. The patient was admitted to the hospital and a rectal examination showed the breech fairly high, cervix about 2 cm. dilated, and contractions every three minutes, lasting twenty-five seconds and of poor quality. Pains continued irregularly throughout the night. By noon the next day the patient showed signs of exhaustion and the cervix was only $2\frac{1}{2}$ fingers dilated. A foot could be palpated through the external os on rectal examination. Contractions seemed to involve portions of the uterus when they occurred and it was felt that uterine contractions were not sufficient to produce complete dilatation or expulsion of the fetus. Temperature had risen to 99.8° F., and the pulse rate was 100. She was given 1,000 c.c. of 5 per cent dextrose in normal saline and prepared for cesarean section twenty-one hours after the onset of labor.

A low flap section was done by one of us (I. T. C.), and a 6-pound 12-ounce female infant was delivered by breech extraction. After closure of the uterus the pelvis was explored and two complete and distinct uteri were found. A normal tube and ovary arose from the lateral cornu of each uterus. The left, nongravid uterus was enlarged nearly two and one-half times and had a small subserosal fibroid on both the anterior and posterior surfaces. The relationship of these two uteri is illustrated (Fig. 1).

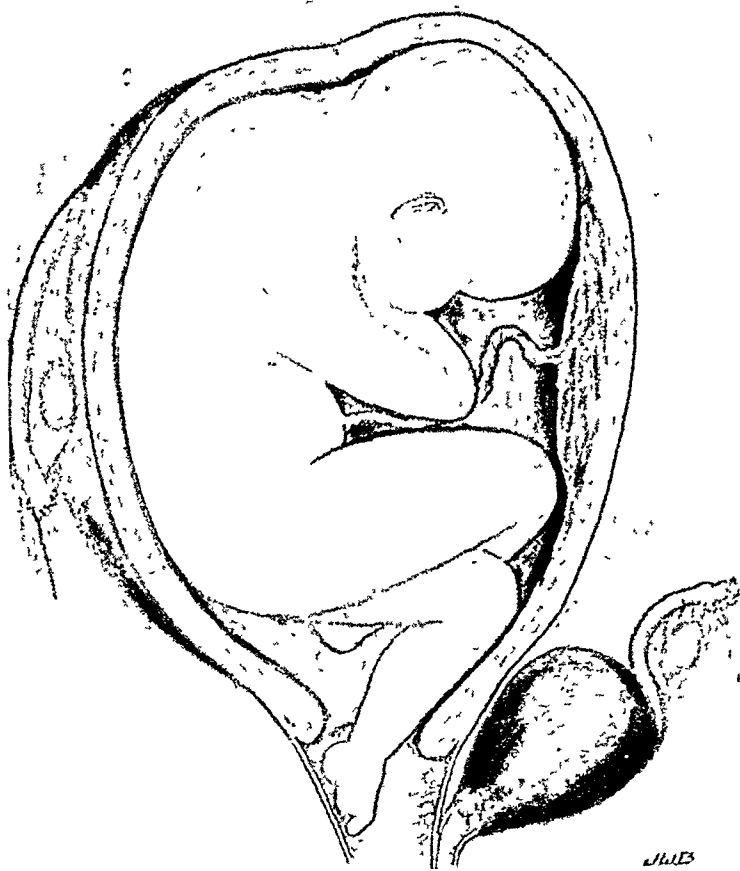


Fig. 1.—Findings on laparotomy. The breech is presenting as a single footling in the right uterus. The left uterus is enlarged and contains small myomas, one of which is visible on the anterior surface.

The patient was returned to her room and given a transfusion of 250 c.c. of citrated blood. Postoperative condition was good. Abdominal distention developed and persisted for several days but was relieved by negative suction, morphine, and a light cradle to the abdomen. Her nurses were cautioned to watch for the passage of the decidual cast from the opposite side with her lochia, but if it ever passed it was not identified as such.

The patient developed a pericarditis with effusion on the fifth postoperative day, but she responded well to 900,000 units of penicillin, calcium, oxygen therapy and 500 c.c. of citrated blood, and the heart shadow slowly returned to normal. An increase in the cardiac dullness to percussion and diminished breath sounds anteriorly were found on physical exam-

ination and an electrocardiogram showed myocardial damage. The patient was discharged from the hospital on the twenty-sixth postoperative day.

A postpartum check on March 14 showed the abdominal scar well healed. Both uteri were about one and one-half times enlarged. The menses had become re-established the week before. The trichomonas infection was rather extensive, and treatment was begun and the patient advised to carry out therapy on both sides of the vaginal septum.

An intravenous pyelogram was done to determine whether any anomalies of the urinary tract existed, but the only abnormal finding was dilatation of the right ureter, a condition commonly encountered in pregnancy and in the early postpartum period.

ACUTE DIVERTICULITIS OF THE SIGMOID IN PREGNANCY

M. D. SCHNALL, M.D., NEW YORK, N. Y., L. E. PHANEUF, M.D., SC.D., AND
J. F. CONWAY, M.D., BOSTON, MASS.

(From the Department of Obstetrics and Gynecology, Carney Hospital)

DIVERTICULITIS is a condition occurring not uncommonly in the female, and some excellent papers have been written on this complication.^{1, 2} However, a review of the literature for the past forty years with the aid of the American College of Surgeons' Library Staff has not revealed the description of a case of acute diverticulitis occurring in pregnancy. It is possible that a number of such cases go undiagnosed and for this reason we point out that in gravid women complaining of left lower quadrant pain, the differential diagnosis should include acute diverticulitis. Following is a case of acute diverticulitis of the sigmoid with abscess formation and spontaneous resolution in pregnancy, labor, and in the puerperium.

The patient, D. M., a 31-year-old primigravida, entered the Carney Hospital on May 22, 1944, complaining of pain in the left lower quadrant of three days' duration. There were no familial tendencies other than that the father died of carcinoma of the bowel. She had no previous illnesses and no operations except tonsillectomy as a child. The systemic review was unusual only in that there had been a lifelong tendency from early childhood toward severe constipation. Occasionally she had gone up to eight days without a bowel movement, and then hard fecal masses were passed.

The menarche was at 18 years and the periods were irregular, coming at one- to four-month intervals. The last menstrual period was on July 23, 1943. The prenatal examinations revealed no pelvic pathology, and the pregnancy, excepting constipation, was free of untoward signs and symptoms except for constipation.

While turning over in bed on May 19, 1944, at 11 P.M., she suddenly experienced a sharp nonradiating pain just medial to the left anterior superior iliac spine, lasting only for a few seconds. Her condition was unchanged until 9 A.M. next day when she felt faint and had an aching sensation diffusely throughout the left lower quadrant. During the next three days pains occurred in the left flank and left lower quadrant every one and one-half to three hours, lasting one-half hour; they were dull at the onset but gradually became sharp. During this time the patient was anorectic; there had been no bowel movement for three days.

At the time of admission to the Carney Hospital on May 22, the physical examination revealed a well-developed and well-nourished white woman somewhat restless in bed but not complaining of pain. The temperature was 98.6° F. pulse 86, respirations 18, and blood pressure 120/60. There were psoriatic lesions over the chest, back, and arms. The head, ears, eyes, nose, and throat appeared normal. Heart and lungs were normal. The breasts were free of masses. The upper abdomen was soft and slightly distended. The liver, spleen, and kidneys could not be palpated. The uterus was enlarged to three fingerbreadths above the umbilicus; the fetus was found to be with the left occiput anterior, the fetal heart tones being 138 and of good quality. Moderate tenderness and spasm were found in the left lower quadrant and flank. Rectal examination disclosed the head well engaged, cervix soft and slightly taken up. Except for lesions of psoriasis the extremities were not remarkable.

A catheterized specimen of urine was reported as of specific gravity 1.020, acid, a trace of albumin, no sugar, no acetone, and 3 white blood cells per high-power field. The hemoglobin was 84 per cent, red blood cells 4,680,000, white blood cells 28,700 with 80 per cent polymorphonuclear leucocytes, 18 per cent lymphocytes, and 2 per cent eosinophiles. The red cells appeared normal. The blood Hinton was negative.

An intravenous pyelogram revealed only mild hydronephrosis on the right with a narrowing at the right ureteropelvic junction. On the left no abnormality was noted.

A diagnosis of possible twisted pedicle of an ovarian cyst or red degeneration of a uterine myoma was entertained until a barium enema was done at 12 noon, May 26. It revealed a fair degree of dilatation of the entire colon and a matting of the bowel in the middle of the sigmoid due to diverticulitis. At 5 P.M. the same day, uterine contractions started and at 9 P.M. the cervix was fully dilated. A left occipitoposterior was rotated manually and the patient was delivered by midforceps and episiotomy of a living female infant of 4½ pounds. This course was chosen to avoid a long second stage with aggravation of the patient's condition. While the patient was under light anesthesia a deep fixed mass 6 cm. in diameter was palpated to the left of and at the level of the umbilicus.

Immediately after the delivery there developed a moderate degree of abdominal distention and the temperature rose to 100.5° F. The patient developed increasing tenderness in the left lower quadrant, vomited several times, and had up to ten liquid bowel movements each day. Intravenous glucose-saline solutions and a Miller-Abbott tube were utilized. The abdominal pain subsided twenty-four hours after delivery, but severe nausea, vomiting, and diarrhea continued. She was losing weight and strength rapidly and could not retain even a few sips of water. Serum proteins were 4.85 Gm. per cent; the white cell count which was 29,400 on May 25 fell to 12,600 on May 30, but on June 3 rose to 25,000. The very few available veins used until now were no longer suitable because of repeated intravenous administrations. On June 4 an infusion was started directly into the medullary portion of the body of the sternum^{3, 4} and by this route glucose-saline solutions, blood plasma, amino acids (Stearn's), and the synthetic B vitamins were given in suitable quantities. After the patient received adequate therapy in this manner, the gravity infusion apparatus was removed from the needle and a stylet inserted into the needle. Next day the stylet was removed from the sternal needle and fluid therapy started again. By June 6 the nausea, vomiting, and diarrhea subsided and since she was able to retain some fluid, the sternal needle was removed. She had rallied rapidly and six days later was out of bed taking a semisolid diet. On June 13 a barium enema and next a gastrointestinal series were done, and these showed no evidence of any abnormality.

The patient was discharged June 16 in good condition. However, a small nontender mass was palpable in the left vault. The white cell count was 16,200. The infant was not discharged until three weeks later when it weighed 5¾ pounds and was in excellent condition.

Subsequently, she was seen on July 13 when examination was negative except for a small nontender mass in the left vault. She said she felt perfectly well. An examination, August 14, revealed that this mass had disappeared. A barium enema was repeated Nov. 21, 1944, and this showed no organic lesion in the large bowel but there was a moderate degree of generalized spasm of the colon.

Apparently the patient had an acute diverticulitis of the sigmoid with abscess formation, inflammatory reaction of the bowel wall, and matting together of adjacent loops of bowel, accounting for the signs and symptoms on admission. However, shortly after the barium enema, labor started and the patient delivered. Thereby the inflammatory reaction was accentuated, the bowel lumen compromised, and marked signs of intestinal obstruction became manifest. However, the condition subsided with conservative treatment.

Summary

A case of acute diverticulitis of the sigmoid occurring at the time of pregnancy, labor, and the puerperium is presented. This condition should be considered in the differential diagnosis of left lower quadrant and left flank pain in the gravid woman. The value of conservative management in this type of case is demonstrated.

References

1. Huston, H.: *Arch. Surg.* 26: 1111, 1933.
2. Wetherell, F. S.: *Tr. Am. Ass. Obst., Gynec. and Abdom. Surg.*, 1937, pp. 43-53.
3. Tocantins, L. M., and O'Neill, J. F.: *Proc. Soc. Exper. Biol. & Med.* 45: 782, 1940.
4. Schnall, M. D., and Heffernan, R. J.: *Am. J. Surg.* 68: 44, 1945.

REACTIVATION OF ENDOMETRIOSIS BY STILBESTROL THERAPY

ROBERT L. FAULKNER, M.D., AND E. A. RIEMENSCHNEIDER, M.D.
CLEVELAND, OHIO

(From the Department of Obstetrics and Gynecology Western Reserve University and University Hospitals)

REMOVAL of both ovaries *usually* stops the progress of endometriosis and results in recession of residual lesions not removed at operation. Such a favorable result does not always follow ablation of ovarian function because in certain instances growth characteristics of the lesions apparently become irreversible before operation is performed. It may not make much difference what is done to these few unfortunate individuals encountered in surgical practice because they are apt to remain pelvic cripples the rest of their lives. However, some interest attaches to the question of therapy with ovarian hormones for menopausal symptoms in those patients in whom endometriosis has been *successfully* treated by castration. The recent excellent review of endometriosis by Scott¹ makes no mention of this phase of the subject. Sanders,² in his discussion of the clinical and therapeutic considerations involved in endometriosis, feels that the postoperative use of theelin does not reactivate the disease nor does it appear to influence the recession of the growths left in the pelvis. However, in his comment on the article about endometriosis by Jenkinson and Brown,³ Greenhill⁴ says, "Is it not conceivable that estrogens could bring about a return of the lesion just as the ovarian secretions produced it before castration?"

There is gained readily a clinical impression that oral estrogens increase the pain and discomfort of residual endometriosis. This observation is perhaps most common in those patients in whom bowel discomfort exists and is not entirely eliminated by operation.

The following case report has a bearing on this subject because the patient presented a more objective symptom than pain.

Report of Case

J. S., a 36-year-old housewife, was first seen on the medical service, June 7, 1940, with the complaint of tarry stools. Her health has been good until three years before admission, since which time she had episodes of bleeding from the bowel serious enough to be followed by weakness and dizziness. During the three years, she had been in other hospitals of Cleveland four times and, in addition to the investigation of the bleeding, had had thirteen transfusions. No cause for intestinal hemorrhage was demonstrated by any clinical, laboratory, or x-ray methods of diagnosis.

After admission to this hospital there was blood in the stools until the thirty-first hospital day. Repeated transfusions partially compensated for the patient's loss of blood by bowel. Again all investigations as to the source of bleeding were fruitless.

On the forty-sixth hospital day the patient was operated upon and thorough exploration of the upper gastrointestinal tract was carried out. No cause for the bleeding was found. Incidental appendectomy was performed.

The patient was readmitted to the hospital on Aug. 5, 1940; Sept. 10, 1940; Jan. 30, 1941; and June 23, 1941. A second exploratory laparotomy was done early in 1941 without positive findings. On each admission many transfusions were necessary to replace blood loss. Proctoscopy was done repeatedly during the year without positive findings.

During December, 1941, one of the medical staff members, reviewing the history of this patient, noticed that each of her gastrointestinal hemorrhages began at the time of a menstrual period. Therefore it was decided, after gynecologic consultation, to explore the patient *once more* and to ablate ovarian function in an effort to stop the periodic gastrointestinal hemorrhages.

The patient was therefore transferred to the gynecologic service where, before operation, a definite diagnosis of endometriosis could not be made upon vaginal or rectal examina-

tion. At operation several small areas of endometriosis were found, however, rather high on the rectum; this was confirmed by biopsy of the lesions and study of the ovaries which were both removed along with the uterus.

The patient was followed in the gynecologic dispensary without incident. Early in June, 1942, she complained of severe hot flushes and stilbestrol was given. She took the stilbestrol for a few days and on June 13, 1942, fainted, became nauseated, and vomited twice. She came at once to the Emergency Room where it was discovered that she was again having rectal bleeding. The red blood count was 2,270,000 and the hemoglobin was 44 per cent (Sahli). By inquiry from the patient it was ascertained that she had taken between ten and fifteen 1 mg. enteric coated diethylstilbestrol tablets in as many days.

Gastrointestinal work-up was again negative, the patient was transfused seven times, stilbestrol therapy was discontinued, and she was discharged from the hospital on the twenty-sixth hospital day.

Since June, 1942, the patient has been followed in the outpatient department and has remained entirely well, flushes being fairly well controlled by sedatives.

Summary

A patient with severe periodic bleeding from endometriosis of the bowel, requiring in all over seventy partial or whole transfusions, is reported. She was finally treated by surgical castration and was well until given diethylstilbestrol for menopausal symptoms when severe recurrence of the bleeding took place. Permanent recovery followed discontinuance of this therapy.

References

1. Scott, Roger B.: *AM. J. OBST. & GYNEC.* 47: 608, 1944.
2. Sanders, R. L.: *Surgery* 13: 239, 1943.
3. Jenkinson, E. L., and Brown, W. H.: *J. A. M. A.* 122: 349, 1943.
4. Greenhill, J. P.: *The 1943 Year Book of Obstetrics and Gynecology*, Chicago, The Year Book Publishers, p. 419 (Comment).

ENDOMETRIOSIS OF THE ABDOMINAL SCAR

LOUIS NEWTON, M.D., BRIDGEPORT, CONN.

MRS. M. R., 27 years old, a white patient, while in service with the Women's Army Corps, on Dec. 26, 1943, developed a sudden urinary retention. This condition cleared up after a few days of catheterization. Thorough urologic investigation did not reveal any pathology in the urinary tract. Another sudden retention occurred on July 13, 1944. At this time she was sent to the Woodrow Wilson General Hospital where another complete urologic investigation was again negative. She was told that "probably a tumor of the womb pressed on the bladder" and received her medical discharge papers.

Careful questioning revealed a perfectly normal menstrual history; the past history contained the significant fact that on Sept. 3, 1934 (at the age of 17 years), she was operated on for a ruptured tubal pregnancy (left side) at the Sydenham Hospital, New York City.

On pelvic examination the fundus of the uterus was found to be somewhat enlarged and irregular, slightly movable, and tender. Another cystoscopic examination revealed normal findings. A diagnosis of subserous fibromyoma of the uterus was made, and at the operation on Aug. 12, 1944, the following were the significant findings:

While excising the abdominal scar of the previous operation, an irregular mass of walnut size and of cartilagenous nature was encountered 2 inches below the umbilicus. Its growth extended into the rectus muscle down to the peritoneum. This entire mass was excised and it contained several small, pea-sized cysts of dark blue color. These upon puncture revealed dark, thick fluid.

When the peritoneal cavity was opened, both the fundus of the uterus and bladder were found to be attached by a thick, irregular band of omental and inflammatory adhesions to the lower angle of the undersurface of the previous abdominal scar. When these adhesions were separated, the uterus was found normal, not containing any fibromyoma.

Microscopic sections revealed endometriosis of the abdominal scar.

Summary

1. A case of endometriosis of the laparotomy scar is presented. In view of the history of ruptured tubal pregnancy, it can be assumed that "soiling" of the abdominal wound occurred at that time during the operative procedure. The histogenesis cannot be proved definitely by this theory. There are various other theories which may explain the occurrence of this comparatively rare condition.

2. The true nature of the pathology could hardly be suspected because the lesion itself was entirely without symptoms.

3. Adhesions of the uterus to the undersurface of the scar containing the area of endometriosis account for the erroneous diagnosis of fibromyoma by three different observers.

4. The urinary retention which occurred on two different occasions may have been neurogenic, but it cannot be adequately explained. Six months later patient was well and will be observed further.

881 LAFAYETTE STREET.

PREGNANCY IN A DIVERTICULUM FROM THE UTERUS

M. C. HAWKINS, JR., B.S., M.D., F.A.C.S., SEARCY, ARK.

(From the Hawkins Clinic Hospital)

MRS. E. C. W., Case No. 45-45, white, aged 29 years, was admitted to the Hawkins Clinic Hospital on January 23, 1945, because of a painful and tender mass in the right lower abdomen. She stated that the onset of pain had been two weeks before and at that time she had discovered a mass in the abdomen. The pain had progressively become more severe and the mass larger. There was no history of fever, nausea, or vomiting. She had been married for eight years, and had had no pregnancies. Menstruation was normal up until Sept. 10, 1944, since which time she had not menstruated. Her past history was essentially negative, with no surgery.

Physical Examination.—Patient appeared anxious and rather disturbed and suffering moderate pain; blood pressure 118/70, pulse rate 80, temperature 98.4° F.; head, neck, eyes, ears, nose, and throat, negative; heart and lungs, negative; breasts, moderately tense, otherwise negative; abdomen, soft, not distended. There was a round, smooth, palpable mass between the umbilicus and the symphysis, to the right of the midline, extending upward from within the pelvis to within 2 inches of the level of the umbilicus. The mass was tender, slightly movable, and firm.

Genitalia: Perineum, normal; vaginal mucosa, bluish discoloration; cervix, softened but otherwise normal. Bimanual: Uterus slightly enlarged and softened and apparently pushed to the left by a tense, sausage-shaped mass of elastic consistency attached to the right superior-lateral portion of the fundus of the uterus, extending from high in the right pelvis to within 2 inches of the level of the umbilicus and movable with the uterus.

Tentative Diagnosis.—Pregnancy complicated by pelvic tumor.

Operation was advised, and on Jan. 23, 1945, the patient was operated upon under cyclopropane and oxygen anesthesia. Through a low midline incision the abdomen was opened, revealing a tense semifluctuant sausage-shaped diverticulum from the uterus, 6 inches in length and 3 inches in diameter, with bluish discoloration at its free end, and apparent thinning of its wall at this area. The diverticulum was a continuation from the fundus of the uterus at its right cornu with a pedicle-like attachment. The right round

ligament and Fallopian tube were attached to its inferior lateral border. The uterus was slightly enlarged and softened, but otherwise appeared normal. There was a small multilocular cystic right ovary. The left ovary was normal.

The right tube, round ligament, and superior portion of the broad ligament were doubly clamped and divided. The diverticulum was clamped at its attachment and severed from the uterus, thus removing the diverticulum with attached right tube and ovary. The uterine wall was closed with continuous suture of Chromic No. 1, and the round and broad ligaments were sutured to the uterus in their normal position. The appendix was removed routinely and the abdomen closed.

Pathologic Report.—Tissues consisted of a smooth, tense, bluish-gray, sausage-shaped saclike structure, with a Fallopian tube and a small multilocular cystic ovary attached. At its pedicled end there was found a communicating opening $\frac{1}{2}$ cm. in diameter. On section, a fetus about 12 weeks old was found. The placenta was attached to the medial wall near the distal end. The fetus appeared normal in development. The thin walls of the sac were of uterine musculature. The wall was markedly thinned at its distal end.

Postoperative Diagnosis.—Pregnancy in a diverticulum from the uterus.

The patient had an uneventful recovery and was discharged from the hospital on the thirteenth postoperative day.

A CASE OF INTERSTITIAL PREGNANCY WITH PERFORATION AND EXTENSIVE INTRAPERITONEAL HEMORRHAGE*

IRVING F. STEIN, M.D., F.A.C.S., CHICAGO, ILL.

INTERSTITIAL pregnancy is indeed a rare condition and comprises only from 1 to 3 per cent of ectopics. According to Grusetz and Polayes,¹ there are only 199 cases of interstitial pregnancy noted in the medical literature up to July, 1943. These authors reported a case of interstitial pregnancy which carried to full term; only three such have been reported previously.

Case Report

Mrs. A. G., aged 37 years, married fourteen years, had one child aged 11 years. Small fibroid was noted at time of delivery. No abortions. Menses: onset at 11 years; regular, 27 to 39 days; five days' duration; moderate in amount; no clots or pain. Last menstrual period, June 14, 1944.

On July 17, five days after the expected period, the patient began to spot and, on July 19, began to flow. After ten days of continuous flow, she consulted a neighborhood physician and was advised to remain in bed. Diagnosis: threatened abortion. Four days later, a dilatation and curettage was performed. Pathology report was "pregnancy tissue." Patient continued bleeding for the next three weeks and consulted the author on August 19 at Michael Reese Hospital. Bimanual examination revealed an irregularly shaped uterus with several definite hard nodules. No adnexal tenderness or swelling was found. Diagnosis was fibroids and recent abortion. The Aschheim-Zondek test was negative.

On August 22 the patient had a severe attack of pain in the left side, and fainted. Examination at the patient's home revealed that she was very pale, with a thready, rapid pulse. The diagnosis of ectopic pregnancy was made and she was taken to Michael Reese Hospital by ambulance. She received 250 c.c. of serum and 500 c.c. of citrated blood. After a satisfactory rise in the blood pressure, laparotomy was performed for "bleeding ectopic pregnancy and fibroids." Upon section, the peritoneal cavity appeared filled with several large clots and liquid blood. The uterus was irregularly enlarged, containing several fibroids from 1 to 5 cm. in diameter. The interstitial portion of the left tube was the seat of a 3 cm. swelling, purple in color, with a small perforation on the posterior aspect from which blood was flowing continuously. The left ovary contained a large corpus luteum. The distal por-

*Presented before a regular meeting of the Chicago Gynecological Society, Oct. 20, 1944.

tion of the tube was normal. A supracervical hysterectomy, including the left adnexa, was performed. The right adnexa were preserved. Another transfusion of 500 c.c. was given.

Pathology Report.—Interstitial pregnancy. Large corpus luteum of the ovary. Proliferating endometrium. Myofibromas of the uterus. Adenomyosis of the uterus.

There was immediate improvement. The postoperative course was satisfactory, and on the twelfth day the patient was ready to be discharged when she developed laryngitis. This was followed by a febrile reaction and an upper respiratory infection which delayed her discharge for two weeks.



Fig. 1.

Comment

Pregnancy in this location usually terminates in extensive rupture of the uterine horn with death of the mother from hemorrhage and shock. The exception is when death of the ovum occurs and a hematoma remains. In the case here reported, an interstitial pregnancy of about five weeks' duration was present in a uterus containing multiple fibroids. *Perforation* into the peritoneal cavity with profuse hemorrhage occurred rather than extensive rupture. Multiple transfusions and supracervical hysterectomy were performed, followed by complete recovery.

Reference

1. Grusetz, M. W., and Polayes, S. H.: AM. J. OBST. & GYNEC. 48: 379, 1944.

A SIMPLE TECHNIQUE FOR PREPARING VAGINAL SMEARS

CAPTAIN B. B. RUBENSTEIN, M.C., A.U.S.,* AND HENRY S. GUTERMAN, M.D.,
CHICAGO, ILL.

(From the Department of Metabolism and Endocrinology, Michael Reese Hospital)

REPORTS from this¹⁻⁴ and other laboratories⁵⁻¹⁰ have indicated the value of vaginal smears as a diagnostic aid in various gynecologic endocrine conditions. Several methods for preparing and staining the smears have been presented,^{4, 5, 12} and comparative studies indicate that each method is adequate.¹² The simple and practical technique of preparing vaginal smears, which has been employed in our laboratory for more than ten years, and which is adaptable to home and office use by the patient and/or the physician, is described in detail at this time. The method is acceptable to patients and they learn the technique readily.

The four easy steps of the technique, (1) preliminary preparation of materials, (2) obtaining cells for the smear, (3) fixation of smear, and (4) staining of smear, require the following materials:

- | | |
|----------------------------------|------------------------------------|
| 1. Plastic tube speculum | 8. Fixative solution— |
| 2. Bacterial wire loop | equal parts of 95 per cent alcohol |
| 3. Glass marking pencil | and ether |
| 4. Microscope slides | 9. 70 per cent alcohol |
| 5. Paper clips | 10. 95 per cent alcohol |
| 6. Mason jar— $\frac{1}{2}$ pint | 11. Shorr stain ¹¹ |
| 7. Coplin jars—3 | 12. Clarite† |

Technique

1. Preliminary Preparation of Materials.—

- Label a clean microscope slide with a glass marking pencil.
- Attach a paper clip to the labeled end of the slide to prevent slides (resting in the fixative) from adhering to one another.
- Open the Mason jar containing fixative solution so that a wet smear may be introduced rapidly.

2. Obtaining Cells for the Smear.—

- Insert the tube speculum, which consists of a plastic contraceptive jelly applicator, into the vagina so that the tip rests in the posterior fornix.
- Insert the bacterial wire loop through the speculum until it comes in contact with the vaginal surface.
- Gently rotate the loop several times and withdraw.

3. Fixation of Smear.—

- Spread the vaginal cells adherent to the loop thinly on the prepared microscope slide.
- Place the slide, while the smear is still wet, into the fixative solution.
- The smear may be stained after remaining in the fixative solution for three minutes, but will not deteriorate even if kept there as long as thirty days. (For the convenience of the patient or physician, the slides may be removed from the fixative, dried, and shipped to the office where the staining of the slides is to be carried out.)

The department is in part supported by the Michael Reese Research Foundation.

*On military leave of absence.

†Obtainable from the Neville Company, Pittsburgh, Pa.

4. *Staining of Smear.*—

- A. Place the slide for one minute into the Coplin jar containing 70 per cent alcohol.
- B. Transfer the slide into the Shorr stain for one minute.
- C. After removing the slide from the Shorr stain, allow the excess stain to drain from the slide, and then dip the slide ten times in 70 per cent alcohol.
- D. Dip the slide ten times in 95 per cent alcohol.
- E. Allow the slide to dry in the air.
- F. A drop of Clarite (clearing agent and protecting cover) is applied to the stained smear.
- G. The smear may be examined immediately after Clarite is applied, although the Clarite hardens gradually in twenty-four hours.

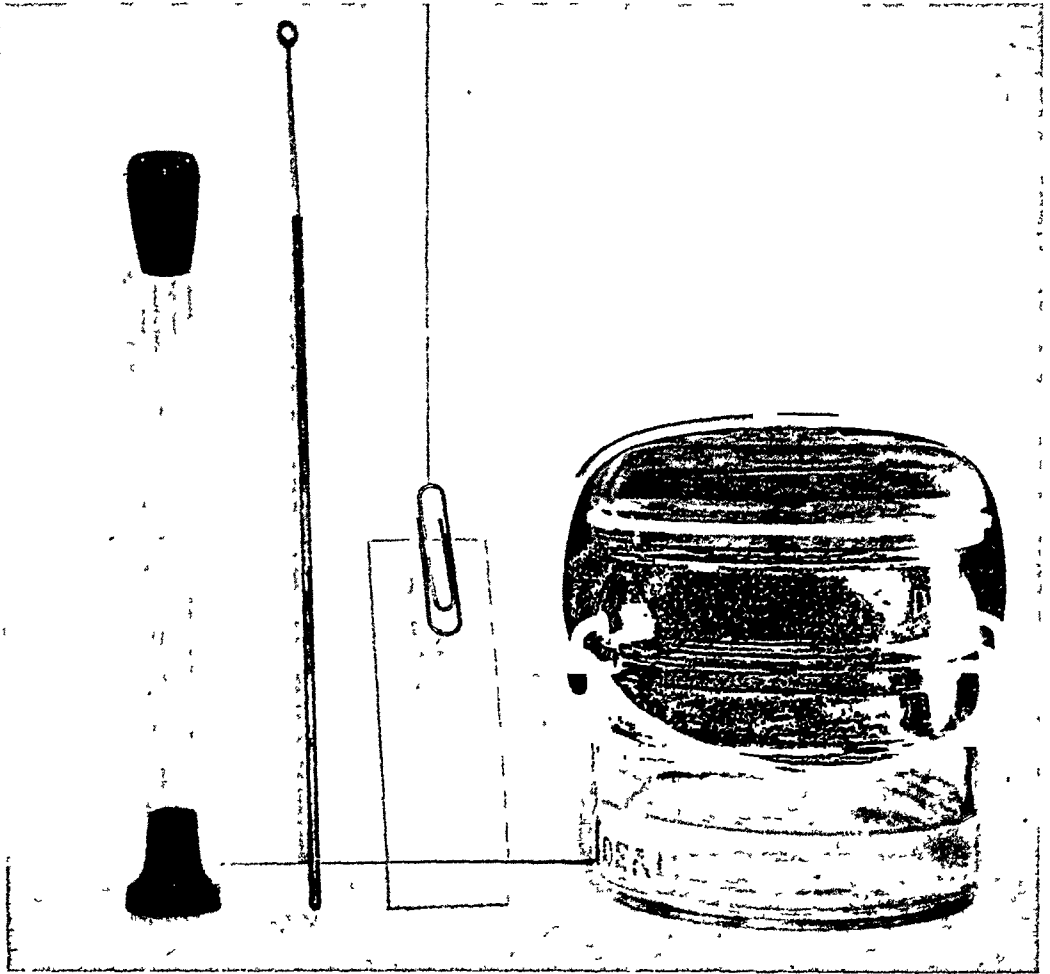


Fig. 1.

The patient who is being instructed how to prepare her own vaginal smears demonstrates to the physician the technique of placing the speculum into the posterior fornix. The importance of placing the slide into the fixative while the smear is still wet, must be impressed upon the physician and patient. The patient can prepare her own smears at home or in the office. The wire loop is sterilized in a gas flame. The tube speculum is washed in soapy water, rinsed, and allowed to dry.

Summary

A simple technique for the preparation of vaginal smears is reported. It is so adaptable that patients can themselves prepare adequate smears at home or in the physician's office.

References

1. Rubenstein, B. B.: *Am. J. Physiol.* 119: 635, 1937.
2. Rubenstein, B. B.: *Endocrinology* 27: 843, 1940.
3. Rubenstein, B. B.: *J. Clin. Endocrinology* 3: 163, 1943.
4. Benedek, T., and Rubenstein, B. B.: *The Sexual Cycle in Women*, from *Psychosomatic Monograph III*, Baltimore, 1942, Williams & Wilkins, Chap. III, p. 31.
5. Papanicolaou, G. N.: *Am. J. Anat.* 52: 519 (supplement), 1933.
6. Papanicolaou, G. N., and Shorr, E.: *AM. J. OBST. & GYNEC.* 31: 806, 1936.
7. Shorr, E., and Papanicolaou, G. N.: *Proc. Soc. Exper. Biol. & Med.* 41: 629, 1939.
8. Salmon, U. J., and Frank, R. T.: *Proc. Soc. Exper. Biol. & Med.* 33: 612, 1936.
9. Campbell, R. E., and Sevringhaus, E. L.: *AM. J. OBST. & GYNEC.* 37: 913, 1939.
10. Krohn, L., Harris, J., and Hechter, O.: *AM. J. OBST. & GYNEC.* 44: 213, 1942.
11. Shorr, E.: *Science* 94: 545, 1941.
12. Mack, H. C.: *J. Clin. Endocrinology* 3: 169, 1943.

MODIFIED APPARATUS FOR TUBAL INSUFFLATION

ROBERT S. MILLEN, M.D., WESTBURY, N. Y.

THE increased cost of medical supplies and the difficulty in having equipment made and repaired prompt me to describe the following apparatus which is simple, inexpensive, unlikely to get out of order, and yet incorporates both the use of a measured amount of carbon dioxide and a standard rate of flow.

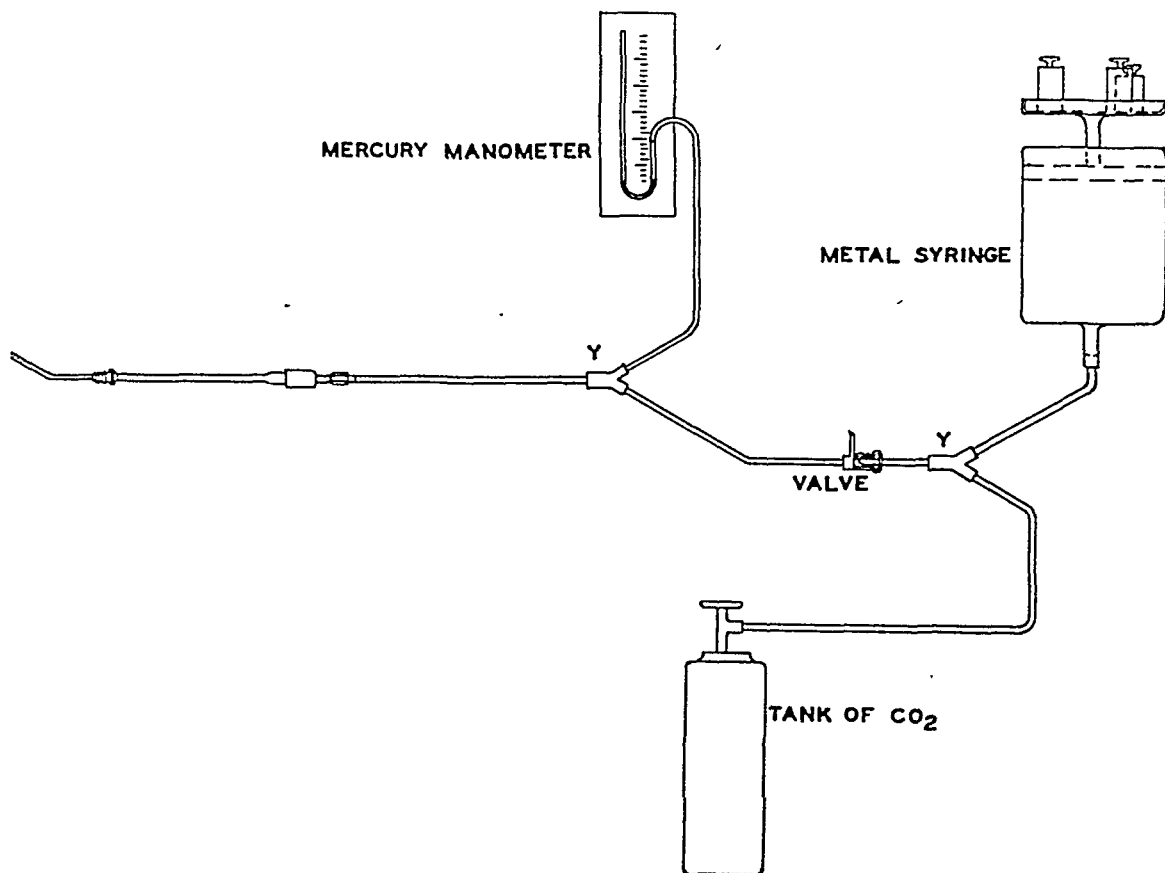


Fig. 1.

The insufflation cannula previously described* is connected by means of rubber tubing and "Y" pieces to a manometer, a tank of carbon dioxide, and a metal syringe that has a tray to hold weights fastened to the handle of the plunger, where there is also a scale to indicate the quantity of gas in the syringe.

*Millen, Robert S., and Jones, Elwood: *AM. J. OBST. & GYNEC.* 41: 340, 1941.

The valve is closed, the tank opened, and a measured amount of carbon dioxide inserted into the syringe. After the cannula has been inserted, the valve is opened and the weight on the handle causes the carbon dioxide to flow through the apparatus. This eliminates the need of a reducing valve. The manometer reading, amount of carbon dioxide used, and rate of flow can readily be determined.

DIFFERENTIAL STETHOSCOPE FOR DETERMINING PATENCY OF EACH TUBE

JOHN FALLON, M.D., JAMES T. BROSNAN, M.D., AND CHARLES F. WHELAN, M.D.,
WORCESTER, MASS.

(From the Fallon Clinic)

TUBAL insufflation can be made a true split function determination by utilizing our ordinary binaural sound-localizing sense to determine the side or sides of origin of the tubal bubble sounds. The enabling apparatus, the differential stethoscope, is a device of early stethoscopists used more often today against submarines than against râles.

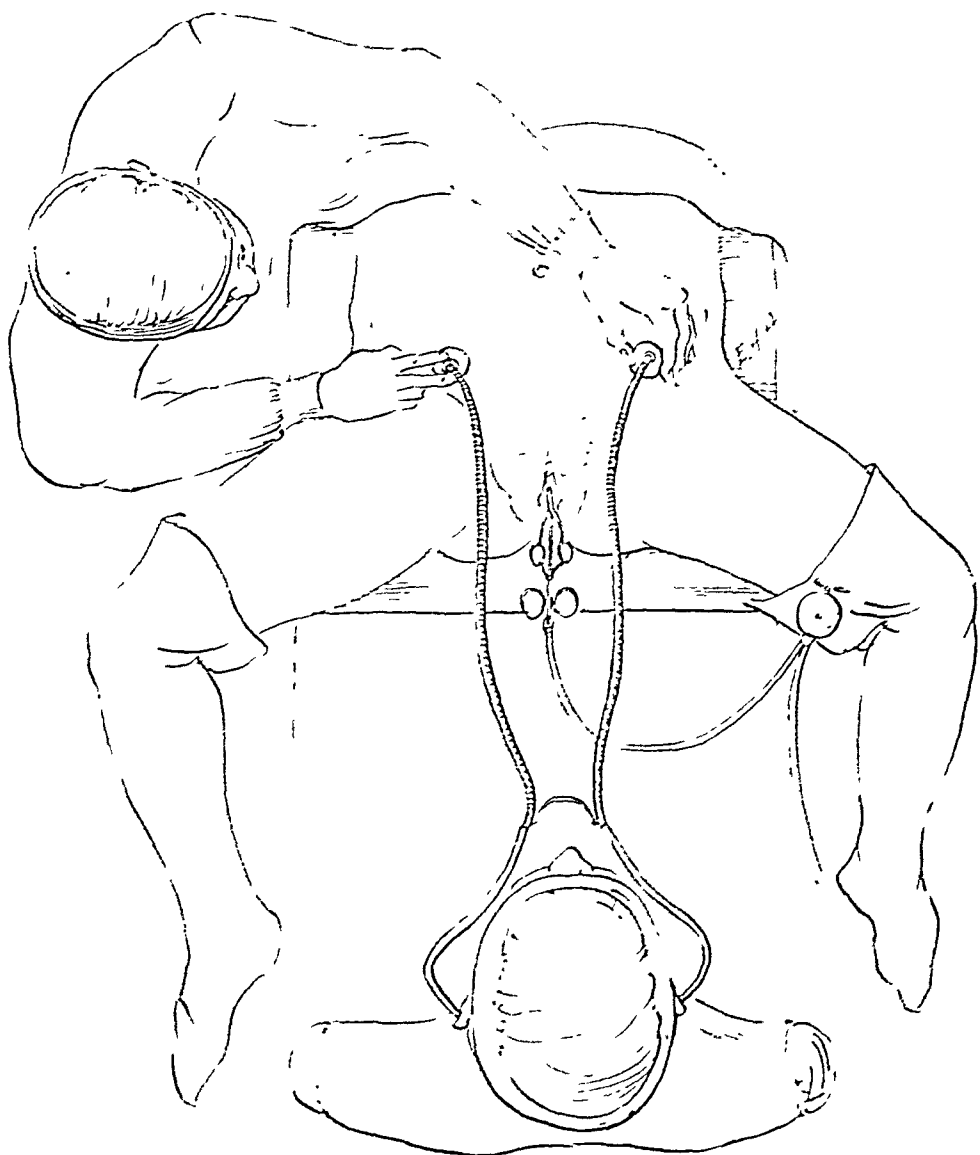


Fig. 1.

The binaural principle allows more precise interpretation than the usual but interpolative method of listening through an ordinary stethoscope placed over one tube after another. Contributing to the interpretation, and fully appreciated only when one has two listening points, are the facts that the tubes often open at different pressures and emit differing sounds.

The interpretation of the test should be unmistakable. Indeed, if it is less than decisive, we advise disregarding it until more is known of the working of the test in various combinations of tubal disease.

Thus far, in five years' use, the interpretations in controls and in the few verified clinical cases have been correct. Predictable sources of error are: (1) fixation of one or both fimbriated extremities near the midline; (2) solid masses between tube and stethoscope; (3) defective binaural sense.

PASSAGE OF A CATHETER THROUGH THE UTERUS INTO THE ABDOMINAL CAVITY

C. A. ELDEN, M.D., ROCHESTER, N. Y.

(From the Department of Obstetrics and Gynecology, University of Rochester School of Medicine and Dentistry, Rochester)

IN A recent issue of this JOURNAL, Bateman¹ presented a case of an attempted abortion using a rubber catheter. His patient visited an abortionist when three and one-half months pregnant, and the catheter used eventually found its way to the abdominal cavity. The pregnancy progressed to term.



Fig. 1.

Of interest is the case of a 34-year-old housewife, C. L., who, having missed her period by one day, inserted a boiled, Lysol soaked, stiff rubber catheter through the cervix. She noticed sharp localized pain just above the symphysis just before it was inserted "deep enough." Bleeding started soon after accompanied by spasmodic pains in the lower abdomen

and "gas pains in the pit of the stomach." The pain continued the next day but the bleeding stopped. The following day, the spasmodic pain changed to pain occurring only prior to voiding, on walking, or when bending over. She became alarmed because she could no longer feel the catheter per vaginam and consulted her physician who could not find it. Abdominal examination was not remarkable at this time. Two days later she developed a tenderness in the lower abdomen and reported a temperature of 100.2° F. Bleeding had resumed. This patient was admitted to the hospital, March 25, 1945, at which time there was definite tenderness in the lower abdomen, the temperature was 37.8° C., white blood count 6,600. An x-ray (Fig. 1) showed the catheter lying in the pelvis, curved below to conform with the lower rim of the pelvis, reaching up and over the right sacral wing, curving laterally with the tip lying in the cecal region.

A laparotomy was done through a Pfannenstiel incision and the catheter was found engulfed by the omentum. The uterus, which was normal in size, was inspected for point of entry, and the only possible site was 1 cm. below the left cornu, anteriorly. Here was found a little fibrin and a depression, but the site did not admit a probe. Ten grams of sulfathiazole were placed in the abdomen before closure, and the patient made an uneventful recovery.

This case illustrates the abuse that a nonpregnant uterus can stand, and that it is not always necessary to do a hysterectomy when a uterus has been perforated.

Reference

1. Bateman, E. J.: AM. J. OBST. & GYNEC. 49: 280, 1945.

Special Article

SOCIAL SERVICE AND CANCER

A Study of 62 Gynecologic Patients

RUTH D. ABRAMS, B.S., M.S., BOSTON, MASS.

(From the Department of Social Service, Massachusetts General Hospital)

LONG illness is so humiliating," said a brilliant young woman dying of a fatal disease. This statement, simply spoken, often came to my mind as medical social worker in the Vincent Memorial Clinic of the Massachusetts General Hospital. Soon I realized that helping patients resolve this and additional feelings of frustration and fear along with the best individual medical social plans were the goals to be reached in as many instances as possible.

During the six-month period beginning Sept. 30, 1943, through March 31, 1944, a total of 273 patients were examined and treated in the Vincent Memorial Clinic of the Massachusetts General Hospital. Ninety-three, or 34 per cent, of these patients were referred to the medical social worker by staff doctors, clinic nurses and secretaries, from outside social agencies, the patients' families, and occasionally by the patients themselves. Of these 93 patients, 62, or 66 per cent, had a proved diagnosis of malignancy. This group of 62 patients known for a minimum of one year were considered for a study because they represented both diagnostically and socially all the patients attending this clinic. Through this study, an attempt was made to test the best case work method applicable.

Inasmuch as the medical social worker is a member of the professional team serving these patients, it is interesting to note the various reasons for social referral. All patients with carcinoma admitted to the wards by the staff or visiting doctors are routinely referred to Social Service. Patients in the terminal stage are also investigated by Social Service. Frequently a nurse refers a particular patient to the social worker to help with transportation, which is a problem because of the often repeated visits to this clinic. Follow-up is one of the secretary's jobs. Should the patient persistently lag, Social Service is notified to clarify to the patient and her family the seriousness of the disease and the importance of treatment so that medical plans will be accepted. The social worker often initiates contact when she notes reasons for its necessity. Since the outbreak of World War II, the Red Cross Home Service, in addition to other social agencies, have referred patients to Social Service.

TABLE I. REASON FOR INITIAL REFERRAL TO SOCIAL SERVICE

Depressed attitude of patient	18
Hospital admission	13
Planning for terminal care	13
Interpretation of illness to patient and family	11
Transportation to and from Clinic	4
Medical report to social agencies	2
Financial difficulty	1
Total	62

Nationality backgrounds of the 62 patients in this study were as follows: Irish, 27; American, 14; Italian, 12; English, 2; Canadian, 2; and one each of the following: American Negro, Armenian, Portuguese, Russian, and Swedish. The largest number of patients was found in the 60- to 70-year group, with the youngest patient 28 and the oldest 78 years. According to their marital status, 28 were married, 24 widowed, 6 single, and 4 divorced or separated. The occupational distribution shows the following: 36 were housewives, 3 domestics, 3 defense workers, 2 dietitians, and one each of the following: bookkeeper,

waitress, camp manager, and school matron. Of the entire group of 62 patients, 14 were unable to carry on any household activities.

Table I shows the 62 patients in this study according to the initial reason for referral to Social Service.

The Vincent Memorial Clinic, with Dr. Joe V. Meigs as Gynecologist in Chief, holds one Gynecological Clinic per week for clinic and semiprivate patients as part of the Tumor Clinic of the Massachusetts General Hospital, which meets daily six times per week. During the time chosen for this study, 15 to 35 patients on the average were seen each Saturday morning. This clinic receives referrals from outside doctors as well as from doctors connected with other clinics within the hospital. From two to four visiting surgeons in addition to one roentgenologist visit this clinic, which is further staffed by a nurse, secretary, and medical social worker.

The medical social worker is the one member of this professional team who has the time to talk with the patient and her family to help make the best possible adjustment to her illness. She also is trained in the knowledge of available social resources. The primary reasons for referral, often quickly dealt with, frequently proved to be the opening wedge for the discussion of other problems related or unrelated to the illness.

Forty-five patients in this series had not been treated previously for their malignancy at this hospital or elsewhere. In other words, these were new patients having been sent from outside local doctors, other clinics in the Massachusetts General Hospital, or elsewhere. In some cases, the diagnosis had already been established, but in none had treatment been started. Therefore, the patient was new to this particular clinic, new to the doctors, social worker, and most of all, new to the experience of suspecting or realizing that she had a "tumor" or a "cancer." Who sent the patient in? Why did she wait to seek medical attention? What does she suspect or know of her medical diagnosis? What does her family know? What is the family's set-up financially or socially? Does it appear possible that she can accept the treatment recommended? These are some of the questions experienced early in the worker's contact with the patient. The worker proceeded cautiously, making sure that she evaluated each patient's reaction to her illness and course of treatment, meanwhile trying to gain the patient's confidence.

With the 17 patients with recurrent disease, the problems were about the same. However, added to those mentioned above was the concern over what the patient knew before and how she reacted to earlier episodes in the same disease. These patients with a recurrent illness usually had a more marked sensitivity than those who were facing this particular illness for the first time. It was more difficult for these patients to accept further treatment when it was known that former ones had not brought about hoped-for cure or lasting relief. Recurrence emphasized and reactivated the individual's dread of again becoming inadequate and dependent.

Inasmuch as the nature of treatment in these cases is prolonged, the social worker has the time to acquaint herself further with the problems encountered by these patients and their families. This affords an opportunity for immediate and long-term therapy and planning. The social worker keeps a record of her findings and plans on a separate sheet which is included on the medical record. (For example, see *Appendix*.)

It is the policy of the doctors in this clinic to explain the nature of the disease to the patient's closest relatives in order to obtain the cooperation which this disease necessitates. As a rule the patient is not told she has a cancer. However, this plan is departed from if the maximum cooperation is impaired, in which case the doctor tells the patient the nature of her disease. Sometimes the social worker has found it desirable to have a particular patient acquainted with her disease and prognosis because she came to believe that lack of knowledge was making the patient more agitated and less confident of herself and the care that she was receiving. In a discussion of what the patient should know, the worker's understanding of the individual patient often was a great help to the doctors upon whom the final decision of telling the patient always rests.

The greatest percentage (58 per cent) of these patients are housewives having the responsibility of their homes, their husbands, and their children. Many represent the pivot around which the home takes shape. These patients are usually not the providers of the home, rather the guardians. Take from the wife or mother her normal duties, either for a short or long period of time, and you have a problem of tremendous personal significance, one which needs readjustment for the patient and for those in the family group. With a prognosis which shifts from "fair" to "guarded" to "poor," the patient is faced with changing her habits of mind and energy which may differ from those where the progress and outcome of the disease is assured. To be of help to these patients, the social worker must know each one as an individual. She must familiarize herself with the patient's home and family, what place she held before illness, and try to understand what the patient knows or suspects, or most important of all, what she wants to know of her illness. It is not difficult to persuade these patients for the most part to go through with their treatment as recommended, for they have confidence in the doctors and know or suspect that they are fighting against a devastating disease and that their sole chance of survival depends upon following the doctor's plan. I have observed that patients and their families are more depressed by the words "no treatment" than anything else, for they understand the implications of that phrase. These patients and their families constantly need encouragement to help them through all the phases of their illness. As far as it is known, varying moods of the patients suffering with a malignant disease do not affect cell growth nor the recurrence of such growth. However, the emotional state of the patient and the understanding of the illness undoubtedly does affect her physical energy and her ability to accept long-term illness, one in which the shadows always remain, no matter what the prognosis may be.

Medical and social replanning is worth while no matter how short or long a period the patient has to live. How to get the mother, wife, or daughter to maintain her role in the family, either partially or wholly, or if this is not possible, at least back to her natural relationship with her family is the job of the medical social worker. No plan of what the patient should know, or for how long she may need help to resume her place in her normal setting can be made until the worker is familiar with the patient's history before her present illness and during her illness. As one doctor so aptly put it, "Help the patient live with herself."

An oft-repeated problem revealed by patients with this disease is the effect the illness and its treatment will have on the marital relationship and the patient's ability to reproduce. It is incredibly common for patients with a malignant condition to suspect that the disease is caused by the marital act. This thought is often shared by the patient's husband or maternal relatives. Feelings of guilt have to be recognized and discussed, as well as the oft-heard opinions that cancer is inherited, something unclean, or possibly of venereal origin. The exact number of cases in this series where these concepts were encountered is not known but they occurred in a sufficient number of cases for the social worker to become increasingly aware of these underlying fears. Recognizing them and reassuring the patient as well as her family over and over again lessened these anxieties and aided in a better adjustment.

At the time of their present illness, fifty-five of these patients lived in a family group and seven lived alone. Although the number of those who lived alone was relatively small, they presented definite factors to be considered. By living alone, whether by choice or circumstance, people often acquire independence. Whenever possible, this independence was maintained. As long as these patients were in the early period of their illness, after the acute period had passed, they were able to carry on at least partially as they had before. However, during the latter stage when the patient was bedridden, placement was often considered necessary. Then a chronic hospital or nursing home was a wiser choice than the family group to which even in good health the patient had become unaccustomed. Also these patients had acquired the habit of living alone and had finally learned to make their own plans. Therefore, the necessity for telling them about their condition became a matter to settle earlier than with the patient who lived in the family group. On the one hand the lone patient

was encouraged to maintain independence as long as possible. However, when her disease approached the terminal stage, she had to be encouraged to become dependent.

For the patient in the family group, the full meaning of the illness was considered at a slower tempo, and plans were made only after full comprehension of the medical and social factors were made known. Those who lived with the patient proved to be of great help to the worker and gave information which could not otherwise have been known.

Immediately following treatment, placement was as follows for the 55 patients who lived in a family group:

- 42 went home
- 8 went for a few weeks to relatives
- 2 went to nursing homes, and
- 3 to nursing homes or chronic hospitals for an indefinite period

With the 7 patients who lived alone, 3 returned to their homes following treatment, and 4 spent a few weeks only in the homes of relatives.

Geographically, the patients were distributed widely:

- 40 came from within a radius of 10 miles
- 7 came from within a radius of 10 to 15 miles
- 10 from 16 miles or more, but in the state of Massachusetts, and
- 5 from out of the state

Transportation problems had to be coped with for, if the trips to and from the hospital were too difficult, the patient would either lag in her treatments or stop entirely. This obviously would prove detrimental to patients for whom there was some hope of cure, arrest of disease, or palliation. The Red Cross Motor Corps in various communities cooperated with Social Service in their requests by giving freely of their services, either for an occasional visit, or repeated visits when daily x-ray treatments were prescribed, which averaged five days weekly for three to five weeks. When transportation could not be arranged, the social worker helped in a selection of a nearby approved* nursing or boarding home from where the Red Cross Motor Corps transportation could function. No patient in this series lagged or discontinued her treatments because of lack of transportation facilities. Transportation was given for fourteen patients during a long daily course of treatment, and for fifteen this service was rendered occasionally. Placement in a nearby nursing or boarding home with transportation was arranged for three patients during a long course of x-ray treatment.

From the medical social worker's point of view, the most significant facts in this study were those related to the patient's ability to resume her former duties, wholly, partially, or not at all, three months after the completion of the prescribed treatment. Naturally, the patient's physical condition had a lot to do with her return to her former duties, but, added to this, an acceptance of the disease emotionally had to be made for return to former activity.

The results from treatment of patients with a cancer of the genital organs were relatively good. Certainly, after prescribed treatment, many patients went along for an indefinite number of months in comparative good health. They were often very sick at the peak of their illness, but once operation or treatment was completed, they returned to relatively good health. In some cases the recurrence of the disease did follow, but often not for several months or longer. The doctors often indicated at the time of examination what the prognosis would be. The immediate results were often good, even when the long-range prognosis was "guarded" or "poor." The medical opinion became the signpost for the worker's interpretation and planning. However, she was prepared to change her plans according to the course of the illness and the varying needs of the patient.

*"Approved" refers to those homes that have been within the year visited by a member of the Social Service Department of the Massachusetts General Hospital and found to be adequate for the care of patients referred for placement.

As was to be expected, the 11 patients with a "fair" prognosis, as noted on the medical record, showed the greatest ability to resume former duties. Actually at the end of the one-year period:

- 4 did their own housework as before
- 4 undertook partial duties
- 3 were unable to perform any of their former occupations

Of the last-mentioned group, it should be added that two could have worked as before had not past emotional difficulties reappeared. This group with a "fair" prognosis were all treated with surgery. As this form of treatment was only attempted when the patient was considered a good operative risk and when it appeared likely to result in a complete eradication of the disease, the social worker was able to take the most optimistic outlook for and with the patient. (For example, see Case 1 in *Appendix*.)

In the second group, which included 24 with a "guarded" prognosis, the following results were noted:

- 8 did all their work as before
- 6 did partial duties, and
- 10 were unable to do anything, either for themselves or in their homes

This group of patients was treated by x-ray therapy followed by radium implantation. They came to the hospital regularly from three to five weeks, five days a week, and then were hospitalized for approximately one week. None failed to complete the treatment recommended.

With "guarded" prognosis and prolonged plan of treatment the worker had to adopt with the patient a middle course to sustain a balance between hope and failure. These patients had to be encouraged to go through with this long and tedious plan. Their changing daily problems, whether related or unrelated to their illness, had to be met. (For example, see Case 2 in *Appendix*.)

There were twenty-seven patients with a "poor" prognosis. These were approaching or had already reached the terminal stage of their illness. For some, palliative treatment was recommended, but in many cases those who had been followed for a long period of time at this hospital or who had come for the first time were given no return appointment. (If appointments were given they were usually made for three months hence and only to satisfy the patient that the doctors were still interested.) To these patients with a "poor" prognosis, the social worker gave not so much hope but reassurance that there was one member of the medical team who was readily available to them or their families in case of need. What the patient should know and what were the resources for placement had to be thoroughly discussed and explained before the patient and her family left the hospital. (The details of the patient's general personality and home situation were kept by the worker so that when, as in so many cases, the patient or her family returned for aid, she had a record of the case and planned accordingly.) Confidence in the worker's interest and ability to help had to be established.

The worker attempted to help patients remain in their homes as long as possible, where plans were made for them to be adequately treated by their local doctors and families. The visiting nurse came as often as requested and proved a great asset to the patient and her family. At the end of the one-year period, eleven of these patients with a "poor" prognosis were living at home, four were in nursing homes, one was in a general hospital, and eleven had died. Of the latter, two died at the Massachusetts General Hospital; two at general hospitals, one at a chronic hospital, three at nursing homes, and three in their own homes.

Meagerness of resources for terminal placements was a major problem. General hospitals discouraged admission. Chronic hospitals had long waiting lists or were located at distances of not less than 40 miles from the patients' homes, and "approved" nursing homes had limited space at a minimum rate of \$25 per week. This limitation of available resources was often a factor in the

choice of how or where the patient was to spend this last period of her life. Although in many instances the worker thought it best for the patient to remain at home, there were cases where placement might have been more advantageous had there been a suitable nursing home or chronic hospital to which the patient could go.

In conclusion, it appears from this study of 62 gynecologic cancer patients that the medical social worker has offered a variety of services which has proved a valuable adjunct in the treatment of the individual patient. By adhering to her specific duties, she was accepted as a member of the clinic group, all of whom were concerned with the best care of the patient. If mental well-being was achieved at the time of treatment and aftercare, then the patient's adjustment to her illness was assured. Certainly, it was to the doctor the patient first gave her greatest confidence. But in many instances the social worker helped to sustain that faith throughout the long and varied period of illness, especially with the terminal cases when the patient felt rejected because no further treatment was recommended.

Appendix

CASE 1.—S. I. *Referral*: Jan. 17, 1944. This patient with a diagnosis of malignancy appeared depressed and desirous of leaving the hospital "against advice." Prognosis "fair."

Social Information (obtained from patient).—Patient is a pleasant woman of 34 years who lives with her husband, son, 13, and daughter, 4 years of age. Patient says that she has nothing to worry about at home, for during her illness and convalescence, her mother has come to stay with her. Patient's husband is a devoted husband and father who earns an adequate wage working in a food market in Vermont.

Patient was told by her local doctor before admission that she had a cancer. It was he who referred her to this hospital.

Action Taken.—It took many short interviews while in the hospital to acquaint patient with hospital routines before she was able to adjust to her new surroundings. She was lonely and needed one friend away from home to whom she could turn for reassurance. Once her dependency was recognized and interpretation of treatment discussed, her spirits rose and she became friendly with all those about her, and remained in ward.

Following surgery, her courage was sustained and she returned home in an optimistic mood.

Follow-Up Note.—April 8, 1944. Patient appeared in the Clinic literally on the arm of her mother. She was found by the doctor to be in good condition. However, patient felt that because of her illness she was unable to pursue her former activities. Worker reassured her of her good health and encouraged her to continue on with her activities as she had before operation.

Sept. 8, 1944.—Patient told worker that since last visit she had resumed all the household activities she did before her illness.

CASE 2.—M. K. *Referral*: March 2, 1944. Because patient was relatively young and the mother of four children, social investigation was considered necessary. Prognosis "guarded."

Social Information.—Patient is a tall, thin, refined girl of 27 years who lives with her husband and four children in pleasant surroundings. Present symptoms had existed for a long time but because of patient's reluctance to leave her home and family, she had failed to seek medical attention. Patient has a quiet dignity and control which commands respect. She has a great many fears about her illness, one of which is that she identified it with that of one of her sons who had a tumor treated at the Children's Hospital which she has suspected was malignant.

Patient's husband works as a machinist for a railroad company. There appear to be no financial difficulties.

Action Taken.—Once interpretation of the illness was given patient's family, they co-operated in helping with the household during patient's hospitalization. Patient herself derived satisfaction from discussing her illness and the differences between her illness and that experienced by her son. Upon discharge from the hospital, patient returned home where after several weeks she was able to resume all her household duties as formerly.

CASE 3.—R. D. *Referral*: Nov. 6, 1943. Patient was referred by visiting surgeon in the Clinic for help and arrangements for future terminal care. Prognosis "poor."

Social Information.—Patient is a young-appearing woman of 54 years who gives the appearance of adequacy in managing her affairs. She is employed in a finance corporation in Lawrence, Massachusetts, in which she has found great satisfaction. She talked of it most enthusiastically as well as of the kindness of her employers. Patient seems to be alone, certainly in this part of the world, and depends entirely upon herself.

Action Taken.—Patient had been told by the doctor just what her condition was, which was that of nearing the terminal stage. She understood what he told her and spoke of it with some feeling which was immediately controlled. Her wish for help was that of knowing in more detail what might happen, but she quickly assumed she would continue her work as long as she could, leaving future plans until later. It was left that she would know she could come here at any time, or could telephone to ask for help in understanding any condition and in making arrangements for palliative treatment. She was told that a local doctor could give her attention and she would find as much help for the moment as to return to the Clinic, thereby saving her strength.

Later: Dec. 17, 1943.—Patient's employer and friend called to say that the time had come for helping and arranging for patient's care. Plan was made for the Rose Hawthorne Lathrop Cancer Hospital in Fall River immediately, where patient died on following day, Dec. 18, 1943.

I gratefully acknowledge advice and help given by Ida M. Cannon, Chief of Social Service, Massachusetts General Hospital, and Dr. Joe V. Meigs, Gynecologist in Chief, Massachusetts General Hospital.

THE DUBLIN LYING-IN (ROTUNDA) HOSPITAL BICENTENARY (1745 TO 1945)

A Short Historical Review of the Life and Work of the Hospital, With Notice
of Its Proposed Bicentennial Congress in Dublin, in 1947

O'DONEL BROWNE, M.A., M.A.O., F.R.C.O.G., F.R.C.P.I.*

IN JULY, 1947, a Bicentennial Congress in Obstetrics will be held in Dublin to commemorate the foundation of the Dublin Lying-in (Rotunda) Hospital. Conditions everywhere are such that justice could not be done to the occasion were the Congress to be held in 1945.

General History, Management, and Development

Although there is a rival claim to the priority, by a few months, in the establishment of the first truly maternity hospital in the world, the Rotunda is undoubtedly the only such institution with an uninterrupted history of service.

Bartholomew Mosse, the son of a country clergyman, was a man without any special qualifications in midwifery, and almost penniless. He realized the need in Dublin for a maternity, or lying-in, hospital for the poor and destitute. Mosse had little influence in Dublin, was in his early thirties, and at that time midwifery everywhere was conducted by the woman midwife—the Sairey Gamp in England, with her counterpart in America, the Hannah Brown. The barber-surgeon, or doctor, was necessary only when the unqualified nurse deemed her patient *in extremis*.

Under these circumstances, with, in addition, widespread poverty, total absence of hygiene and complete ignorance of any refinements such as only became known a century later regarding the nature of puerperal fever and the use of anesthesia, Mosse began his venture.

Mosse opened the original Rotunda in a building in George's Lane, later (and now) South Great George's Street, Dublin, with only a few beds. This was on March 15, 1745, but later, on May 18, 1745, there were ten beds available. He was helped by twelve friends, each of whom became one of the original Governors of the Rotunda Hospital, and, despite all prejudices, the poor lying-in women quickly availed themselves of the facilities Mosse offered. To such good purpose did Mosse and his Governors turn their energies that 3,975 women were delivered in the twelve and a half years of the life of the original Rotunda.

Lack of money was always Mosse's greatest worry. His own small fortune was quickly exhausted; the subscriptions of his original Governors soon became inadequate, and recourse to monies received from lotteries became necessary. Such insecure foundations would have deterred a less courageous man

*King's Professor of Midwifery, Trinity College, Dublin; ex-Assistant Master, Rotunda Hospital, Dublin; Gynaecologist, Sir Patrick Dun's and Monkstown Hospitals, Dublin.

NOTE: The Editors of the JOURNAL feel that by the inclusion of this article in our pages we are paying a well-deserved tribute from the American medical profession to this renowned institution which many of its members have visited as observers and students. This notable and uninterrupted career of service for a period of two centuries constitutes not one but many milestones in the development of obstetrics and gynecology and merits the felicitations and good wishes which the JOURNAL is pleased to extend on this occasion.

than Mosse, but his success despite difficulties, and the knowledge that he was relieving the poor and destitute spurred him on to a further and even greater effort. Still almost penniless, and with no financial or other guarantee of security, he visualized a 150-bed lying-in hospital, which was to be erected outside the then City of Dublin. Three years after the foundation of the original Rotunda, Mosse acquired four and a quarter acres of land on the north side of the river Liffey, in the so-called Barley Fields, and immediately built a wall around his property. The wall was later removed (1785) and the railings which are there today were erected instead. Thus, while Mosse continued to supervise the work in his original Dublin Lying-in Hospital, he undertook the construction of the new Rotunda, the building which, in greater part, is in active service today. There are, of course, more recent buildings which were added from time to time to Mosse's hospital.

Mosse employed the best-known architect of that time, Richard Castle (or Cassels), to design his new hospital. Without delay, wooden coffee-stalls and amusement halls were erected on the newly acquired site. Mosse pursued lotteries further, to the extent of being imprisoned on one occasion; he applied on several occasions for aid from the Government, finally with success in 1756, when not only the Hospital but Mosse himself received assistance. Meanwhile, Castle died; the new building, built to Mosse's design and in the most expensive taste as to interior decoration and quality throughout, progressed. And, throughout these trials and vexations, Mosse not only conducted his own affairs but continued to supervise the old and new hospitals, while petitioning repeatedly for official recognition of his venture.

Perseverance was at last rewarded. The new Rotunda was formally opened on Thursday, Dec. 8, 1757, by the then Lord Lieutenant of Ireland, attended by her Grace the Duchess of Bedford. The old Rotunda was then closed, and its record of 3,975 cases with only forty-four maternal deaths in twelve and a half years, was one of which its founder might be proud. A Royal Charter was granted to the new Hospital on June 16, 1752, but was not signed until Dec. 2, 1756. By then Mosse had formulated the rules whereby the Rotunda is governed to this day.

According to Royal Charter, Mosse was appointed as the first, and only, Master for Life. Subsequent Masters have been appointed for seven years only from those who had completed their three years as Assistant to the Master. The Masters have (with one possible exception) always been resident within the building; but the Master and his Assistants are not whole-time officers, being permitted to conduct their private practices.

In this way there began the Mastership system in Dublin. This still operates satisfactorily, despite the passing of time and the many criticisms leveled at it. When, in 1829, the Coombe Maternity Hospital began in Dublin, it also adopted the Mastership system; so did the third and last Maternity Hospital (now the National Maternity, or Holles' Street Hospital) founded in 1894. But the Rotunda is the only one of the three in which the Master is necessarily resident within the building during his term of office.

Those who criticize the Mastership system maintain that a Master's period of office should be longer than seven years and that he should occupy the Chair of Obstetrics, and/or Gynecology, in a university at the same time. In this way he would be in a position to teach both clinically and academically for a longer period, but, although there have been a few instances when the one man has held the two offices concurrently, and there is now no regulation against it, this has rarely happened.

In reviewing the two hundred years of the life of the Rotunda Hospital, one cannot say that the Charter was unwise; seven years prove a Master's worth, or reveal his shortcomings. Although at the end of the seven years an outgoing Master is rarely more than 55 years of age, those who have contributed something of lasting worth in the advance of their specialty, either during their Mastership or afterwards, may be counted on the fingers of one hand. There have been twenty-eight Masters to date.

Mosse was not only a far-seeing and selfless philanthropist, but a wise organizer. With few exceptions, such as the creation of so-called Clinical Clerks (Extern Maternity Assistants) who administer the Extern Maternity service of the Hospital (of much later date), and the recent tendency to retain the ex-Assistant Masters in charge of the now large, and still increasing, antenatal and other departments, Mosse's plans are still in operation.



Fig. 1.—An unusual wash drawing of the Rotunda in 1783-84. The interesting points shown are the wall around the Hospital boundary and the original Round Room, on right. Shortly afterward, the Round Room was modified, the wall replaced by iron railings, and the assembly rooms built on behind the Round Room. Both the Round and Assembly rooms were built for entertainments, and still yield income to the Hospital. (Reproduced by kind permission of Dr. Bethel Solomons, owner of the original.)

Assistant Masters are chosen by the Master, and approved by the Board, from those who have been Clinical Clerks. The Assistant Mastership is a three-year appointment, renewable yearly at the discretion of the Master and his Board, during which the Assistant Master pays the Master £100 yearly. He is, however, allowed to earn what he can from private practice and from private tuition. The Assistant Master must also pay his maintenance in the Hospital, is responsible for all such work and routine teaching as the Master may allocate to him, and, in the Master's absence, the Senior Assistant acts in his stead. The Assistant Masters alternate the maternity and gynecologic duties monthly; the Assistant Master on gynecology assists at, or performs, the gynecologic operations, but the Assistant Master on midwifery duty only assists at cesarean sections.

Unfortunately, Mosse's Mastership ended, with his death in February, 1759, before his ambitions were realized. He had planned for a 150-bed hospital; even now, when some 3,800 women are delivered annually within the Hospital, there are only 114 maternity beds. The famous Rotunda Round

Rooms, begun in 1764 and completed in 1767, and designed to yield an income for the Hospital, were part of Mosse's scheme. From these Round Rooms, the name "Rotunda" arose.



Fig. 2.—The Rotunda Hospital 1945. This view of the front does not include the new rooms, which are outside the right-hand edge of the photograph. From right to left are the Round Rooms, the main building (puerperal wards and administrative unit), the students' quarters (extreme left), and the porter's lodge with patients' entrance. The labor wards, gynecologic and out-patients' departments, nurses' home, and Rotunda Gardens lie behind the main building.

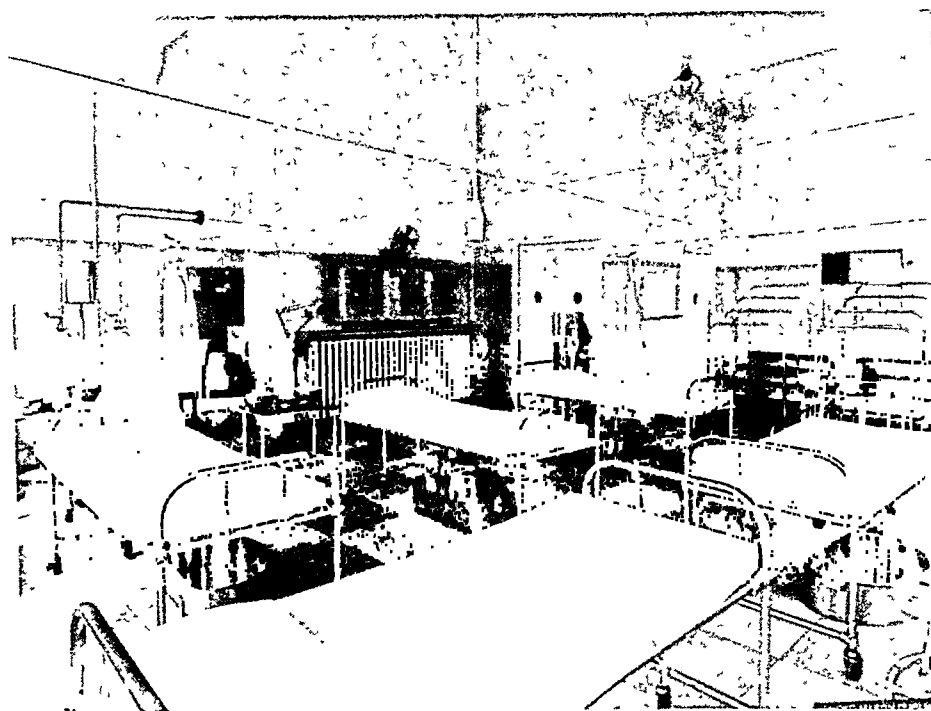


Fig. 3.—The present (1944) Labour Ward, showing delivery couches, students' gallery (moveable) and entrance, sterilizing room (on left), clerical room with window opening into labor ward. A similar unit lies beyond the clerical room and is used as a waiting ward for those in the early stages of labor. The overhead wires seen in the labor ward are used to hang three-quarter length curtains between the couches when many deliveries are in progress.

Since Mosse's death the financial difficulty has continued. Bazaars, personal collections, generous donations by private individuals, fees from nurse probationers, collections on Hospital Sundays, and small contributions from the patients themselves always have been the sources of income, except for the Government grants in the early years of the life of the new Rotunda. Since the Governors agreed to participate in the funds available from the Irish Hospitals Sweepstake in July, 1931, more money has been available, and the Rotunda is now completely up to date, both structurally and in all other respects.

Medical History and Achievements

In the past two hundred years, some thousands of students, doctors, and nurses have studied midwifery in the Rotunda. Its name is known throughout the world, and its teachings, stamped with conservatism, have been a guarantee everywhere of what is sound and right. No institution can hope to be always the Mecca of those who thirst for knowledge, and the Rotunda can boast of prolonged popularity more for the soundness of its practices than the brilliance of its individual Masters.

It is only natural that there should have been bad and good Masters. The Mastership system prevents the bad Master doing more than immediate harm; the outstandingly good Master sets a fashion which either produces an immediate improvement or, at least, prolongs and adds to the good points of his predecessors.

Mosse himself contributed nothing to medical literature, but he is undoubtedly one of the great men, possibly the greatest, in the history of the Rotunda. He was succeeded by one of his Assistants, Fielding Ould, later knighted in 1760. His book, *A Treatise of Midwifery* (in three parts), published in Dublin in 1742, was a classic, and Ould was regarded by his contemporaries as an outstanding authority.

Ould (Master from 1759 to 1766) was responsible for the use of version in cases of difficulty arising from minor degrees of contracted pelvis. He pointed out that Mauriceau of Paris was wrong in his description of how the head engaged in labor in a case with flattened pelvis, and showed that the sagittal diameter lay in the transverse of the brim in such cases. He also gave the first lucid, though incomplete, account of the technique used in expressing the placenta from the vagina in the normal third stage of labor, and drew attention to the fact that hypertrophy of the uterine muscle wall occurred during pregnancy. His Mastership coincided with the early days of the forceps; he approved of them and probably owned and used a pair. William Smellie regarded Ould as a recognized authority, and for the mutilating operations of that era Ould's *terebra occulta* was considered as an improvement on the crotchet, the vectis, and the various hooks and perforators.

Shortly afterwards, Joseph Clarke became Master (1786 to 1793). He, too, was outstanding and quickly realizing that there was an obvious cause for the excessively high neonatal death rate (1 in 7.7), took steps to improve the ventilation of the hospital. He was rewarded by the immediate lessening of the neonatal death rate to 1 in 15.2.

Clarke also added to, in fact completed, Ould's description of the conduct of the normal third stage of labor. Thus Clarke and Ould between them introduced what is now widely known as the Rotunda (or Dublin) method of expression of the normally separated placenta from the vagina. Karl Cr  d   later described the forcible expression of the placenta from the uterine cavity.

Throughout the period reviewed, puerperal fever was a scourge, against and about which little was known. This was so everywhere. Robert Collins (Master from 1826 to 1833) expressed his views on the pestilence in no uncertain terms and, although he could not give any convincing reasons for his action, instituted regular closure in rotation of the various puerperal wards. When closed, the wards were treated with chloride of lime, lime washings of the walls, scourings, thorough ventilation, new bed linen, and other precautions of which we would now approve. Typhus fever, dysentery, Asiatic cholera, and erysipelas were endemic and epidemic. During these outbreaks, Clarke and other Masters

realized the incidence of puerperal fever was greater, and from time to time patients were advised to stay in their own homes rather than enter the hospital to be confined therein. Thus Collins, without knowing it, was very near the truth and solution of the problem.

It was in such circumstances in the Rotunda that the maternal death rate from puerperal fever at times rose to 1 in every 14 deliveries. At this time, too, the fever in hospitals in England and on the Continent claimed even more victims. Von Arneth, an ex-Assistant of Carl Braun's Klinik in Vienna, visited the Rotunda and other leading centers in England and other countries, and reported that the Rotunda results were best.

A very prolonged and heated debate, arising from a paper by Every Kennedy (Master from 1833 to 1840) and lasting fourteen evenings, raged in Dublin over his suggestion as to the advisability of closing the Rotunda and re-opening it in the form of small three-bedded chalets built within the Hospital grounds. This was rejected by his medical brethren and by the Rotunda Governors, and the doctrine of Semmelweiss, who was prevented in his intention to visit the Rotunda, gradually prevailed. The knowledge he imparted took at least twenty years to be applied here and in the British Isles, largely due to stubborn resistance from the majority and, we regret to say, from several Rotunda officers, past and present, at that time. In America, Oliver Wendell Holmes preached Semmelweiss' doctrine, as did Sir James Y. Simpson in Edinburgh and Edward William Murphy (late of the Rotunda) in London, but Meigs of Philadelphia, Hodge of Pennsylvania, and others elsewhere were not to be persuaded, and it took time to neutralize their influence.

Much the same thing happened with regard to the introduction of anesthesia into midwifery. Here, Meigs again opposed Simpson, but eventually opposition was overcome. Robert Shekleton, then Master of the Rotunda (1847 to 1854), quickly but cautiously tried the novel "chloroform," approved it in certain cases, used it when operative intervention was needed (forceps, version, perforation, etc.), and ventured to employ it to control "the fits" (eclampsia).

Every Kennedy and his Assistants were among the first to record the value of auscultation of the fetal heart in labor. Their observations were very accurate.

The advances from 1845 onward were painfully slow—but they were slow elsewhere. The Rotunda was, at times, backward in some respects, especially in operative gynecology. It must be remembered, however, that the Rotunda was from the beginning, and is today, primarily a maternity hospital. Despite this, the Gynaecological Department, though small, is now a very important unit, and is a recognized center of teaching in this specialty.

Rapid progress occurred when Arthur Vernon Macan became Master (1882 to 1889). In a few short months he instituted all such antiseptic precautions as were known; namely, regular recordings of the temperature and pulse, limited internal examinations, and abolition of the communal marine sponge as the means of washing up patients. He preached the value of careful palpation of the abdomen and of early rising after childbirth. In 1890 Macan was able to record that he had done the first successful cesarean section (classical) in the Hospital. He also approved the axis traction apparatus invented by his Assistant, William C. Neville, for use with the Barnes' forceps.

By this time the Extern Maternity Department had become extensive, and two fully qualified Extern Maternity Assistants (Clinical Clerks) a necessity.

William Smyly (Master from 1889 to 1896), later knighted, was an ideal successor to Macan. Small in stature but big in outlook, cultured and devoted

to his work, observant, tireless, and of infinite patience, he added the finishing touches to what Macan had begun. With the aid of a new Matron, from St. Thomas' Hospital, London, he began the Rotunda Nurses' Training Scheme, and in his time the standard of the nurse's life in the Hospital, and of her qualifications, left little to be desired.

Smyly traveled widely both during and after his Mastership. From wherever he had been, he brought back and applied all that was best. His exertions resulted in the building of an Auxiliary (mostly gynecologic) Hospital to the existing Rotunda; the establishment of two new labor wards; the regular publication of annual clinical reports (hitherto sporadic); and the maintenance of the highest standards of midwifery practice and teaching, with the introduction of a new operative era of gynecology. In his time, eclampsia, and eclampsism (or pre-eclampsia) became recognized as a serious complication, and efforts were made to combat it. He was tireless, too, in the struggle against puerperal fever and opposed cesarean section and other lesser intervention in midwifery.

One of Smyly's Assistants, Ernest Hastings Tweedy, became Master later (1903 to 1910). When Assistant to Smyly he stated his views on eclampsia (1896), and on becoming Master put his views to the test. He reduced the maternal mortality rate from eclampsia from 15-20 per cent to 8 per cent, a truly remarkable achievement. That it was no chance was clearly shown later when Henry Jellett (Master from 1910 to 1914 and again from 1917 to 1919) was on active service in the first World War, and Tweedy assumed joint control of the Rotunda with Smyly and another ex-Master, Purefoy. The good results obtained by Tweedy during his own Mastership (1903 to 1910) had not been maintained after his Mastership had ended, but when his treatment was again adopted in full detail, his last results were even better than those he had previously obtained. The Tweedy, Rotunda, or conservative treatment of eclampsia needs no formal introduction. It is widely known in every medical community, and the only other treatment followed at present (also strictly conservative in nature) is that of Stroganoff.

Tweedy did much for the Rotunda. The maternal mortality rate for his seven years of office (0.351 per cent) was, and is to date, the lowest ever recorded for a *complete* Mastership. This was accomplished despite seven deaths from puerperal fever in the first year, the result of an epidemic which was raging when he assumed office, and without the advantages we have enjoyed from chemotherapy since 1936.

Tweedy was the worthy recipient of the coveted degrees of M.D. Hon. Causâ of Dublin University (1923), the no less distinguished Honorary Fellowship of the Royal Academy of Medicine in Ireland (1923), and became the twelfth Honorary Fellow of the Royal College of Obstetricians and Gynaecologists, in 1944. He died on Jan. 22, 1945.

Gibbon FitzGibbon's Mastership (1919 to 1926) took place during the "troubled times" which followed the end of the first World War. Beset by financial difficulties and hampered by the Civil War, FitzGibbon showed resourcefulness and maintained throughout the high standards of the Hospital.

FitzGibbon is especially to be congratulated upon having restored the finances of the Hospital, opening the Antenatal Department, putting induction of labor in cases of contracted pelvis on a sound footing, recognizing new facts concerning accidental hemorrhage, and stressing the importance of external podalic version when placenta previa was to be treated by the bringing down of a leg. He, too, was one of the first to attack the problem of puerperal fever on modern lines, and carried out an investigation on the subject in conjunction with J. W. Bigger, Professor of Bacteriology in Trinity College, Dublin.

Bethel Solomons (Master from 1926 to 1933) followed FitzGibbon and was largely responsible for influencing the Governors of the Rotunda to participate in the Irish Hospital Sweepstake funds. Although Solomons had by his own energies collected a large sum of money, this was not sufficient for the ambitious plan he envisaged. The additional monies derived from the Hospitals Sweepstake Commission made his schemes possible. New operating theaters, new accommodation for nurses and sisters, improvements in the students' residence, the installation of an x-ray department, and the reopening of the pathologic department, all these and other structural improvements were planned and mostly completed before his Mastership ended. The remainder of Solomons' scheme and further improvements were completed during his successor's term of office.

No Master has produced better results in the treatment of placenta previa than Solomons, and in his 147 cases of proved placenta previa there were only two maternal deaths, a percentage mortality of 1.36 per cent.

Tireless in his efforts, by his example Solomons inspired those who worked with him, and the teaching facilities within the Hospital rose to a very high level.

In 1934 Solomons received the Honorary Fellowship of the American College of Surgeons, the Honorary Fellowship of the American Association of Gynaecologists and Abdominal Surgeons, and the Honorary Fellowship of the Central Association of Obstetricians of America.

To Andrew H. Davidson (Master from 1933 to 1940) it fell to complete such plans and alterations as were begun by Solomons, and to plan and bring to completion his own ideas. Not only did he and his Assistants maintain a high standard of teaching and practice in the Hospital, but did so under great difficulty owing to the fact that builders, painters, electricians, and other technicians were constantly on the premises.

Prior to the introduction of Prontosil, in 1936, the Hospital was visited by a severe outbreak of hemolytic streptococcal puerperal fever. The investigation of the possible sources of infection and the steps taken to check the disease and prevent its recurrence were carried out in a painstaking, methodical manner, and on the most modern lines.

Davidson quickly assimilated all new knowledge from other centers, and with his up-to-date x-ray equipment he studied the pelvic architecture and was able to confirm and, in some ways, add to the conclusions of the two American workers, Caldwell and Moloy.

This Master, too, carried out most excellent gynecologic plastic surgery, and is recognized as a leader in the operation of vaginal hysterectomy.

Under the present Master, Ninian Falkiner (1940-), all the highest traditions of the Hospital are being maintained, despite the difficulties of food, fuel, lighting, transport, etc., which exist here today.

The teaching of students and postgraduates is of the highest order, and the new students' and postgraduate quarters are always full.

Falkiner's original work on the early human ovum, the corpus luteum, the circulation within the placenta, and other problems, is widely known, and as a result of his influence, every encouragement is being given to research under skilled direction.

Within the last twenty years 52,203 women have been delivered in the Rotunda with a maternal mortality rate of 0.51 per cent. The Hospital is working strongly and efficiently, and Bartholomew Mosse has no need to regret his venture.

Department of Reviews and Abstracts

Selected Abstracts

The Newborn

Miller, Herbert C., Johnson, Roswell D., and Durlacher, Stanley H.: A Comparison of Newborn Infants With Erythroblastosis Fetalis With Those Born to Diabetic Mothers, *J. Pediat.* 24: 603, 1944.

During the past decade, hydrops fetalis, congenital anemia of the newborn, and icterus gravis have been considered as parts of a single syndrome, because they were found to have a familial incidence.

Recently Levine and his co-workers have held firmly that the syndrome and its familial pattern are dependent on iso-agglutinins developed in the mother during pregnancy. It has been difficult to reconcile the theory with the fact that about 10 per cent of the mothers are Rh positive, that in some mothers who are Rh negative no isoagglutinins can be demonstrated in spite of the fact that their infants have erythroblastosis fetalis, and that there is no correlation between the severity of the syndrome in the infant and the antibody content of the maternal serum. The authors present data to show why the iso-immunization theory may not hold in all cases that are diagnosed as erythroblastosis fetalis.

The somatic and visceral changes seen in some infants born to diabetic mothers are similar to those seen in some infants with erythroblastosis fetalis. These changes are normoblastemia, extensive extramedullary erythropoiesis, a hypertrophy of the heart, hyperplasia of the islands of Langerhans, adrenal enlargement, edema, macrosomia, and a tendency to hemorrhage in all the tissues of the body.

There are two striking differences between the two groups of infants. Infants with erythroblastosis fetalis frequently have anemia and jaundice, and the Rh factor in the mother's blood is negative. Infants born to diabetic mothers rarely have anemia or jaundice and the distribution of the Rh factor in their mothers is similar to that in the population at large.

The relationship of the Rh factor in the mother to similarities and differences in these two groups of infants is discussed.

JAMES P. MARR.

De Costa, Clovis Corrêa: Stillbirth in the National Brazilian Institute of Puericulture, *An. brasil. de ginec.* 18: 25, 1944.

The author found that from 1940 to 1943 there were 116 fetal deaths in 1,137 deliveries, an incidence of 14.2 per cent. He reviews the different factors regarded as responsible for the stillbirths and considers failure of the women to report to the outpatient department during the early months of pregnancy the major cause of this high mortality rate.

Pregnancy, Complications, etc.

de Rezende, Jorge: Fibromyomas and Pregnancy, *Rev. de ginec. e d'obst.* 38: 30, 1944.

The author shows that it is not always possible to follow the same line of conduct and he reports three cases to prove it. In the first he performed a hysterectomy during labor because the tumor obstructed the passage of the fetus; in the second in which the uterus was studded with tumors, cesarean section only was performed;

in the third, myomectomy of a pedunculated tumor was done during the fourth month of pregnancy which continued to term and resulted in spontaneous delivery.

The incidence of fibromyoma and pregnancy was estimated by Albrecht at 1 per cent, which seems too low. Many cases escape the statistics because the pregnant woman has a small tumor which passes unnoticed. Other causes are the age of the patients, as the tumors are usually observed in the forties when pregnancy is exceptional, and sterility, which is the cause or consequence of fibromatosis. Peralta Ramos and Bazin assert that pregnancy is relatively frequent in uteri with one or several intramural or subserous myomas, and cite as proof their 156 cases among 27,393 admissions.

Two phenomena increase the interest of the second case and probably contributed to the cure of the patient: the spontaneous expulsion of various necrobiotic fibromatous nodules during the postoperative period and the self-healing action of the puerperal state which forces the tumors to regress and nearly disappear during the involutive stage.

J. P. GREENHILL.

Campos, Aristides: Uterine Fibromyoma and Pregnancy, *Rev. de ginec. e d'obst.* 38: 42, 1944.

The author states that fibromas of the uterus frequently cause sterility which Recasens attributes to mechanical action impeding conception and to changes in the uterine mucosa preventing nidation of the ovum. Pregnancy is not impossible, however, although it is relatively rare.

The growth impulse experienced by the uterus as the result of pregnancy has great repercussion on these tumors. They appear to receive the same hypertrophic and hyperplastic impulse as the uterine fibers, so that fibromas which are hardly recognizable in the empty uterus acquire a considerable volume. Not only hypertrophy of the muscle fibers but also greater vascularization and serous infiltration of its elements contribute to the increase in volume of the tumors. This growth is more marked during the first five months of pregnancy than during the last four, hypertrophy predominating in the first period and serous infiltration in the last.

The tumor may cause abortion, hemorrhage, abnormal presentation, and even impediment to the passage of the fetus. Expectant treatment is advised by most authors because the life of the patient is not threatened. Roentgen therapy cannot be used. If the tumor is pedunculated or can be enucleated, myomectomy is the most conservative intervention and allows the pregnancy to go to term. The author reports a case in which the rapid growth and size of the tumor and the disturbances which it caused required immediate surgical intervention.

J. P. GREENHILL.

Ramirez Bravo, C.: Tumors and Pregnancy, *Rev. de ginec. e d'obst.* 38: 12, 1944.

The cases observed by the author at the Maternity of the National Hospital of Santiago, Chile, show that uterine fibromyomas, ovarian cysts and other tumors which, by their localization can produce dystocia must be removed at a time as remote as possible from labor. From the obstetric point of view, the future of the myomectomized uterus depends on the number, location, and orientation of the scars. Multiple myomectomies predispose to abortion. Irregular cicatrization of the uterus which has been subjected to several myomectomies predisposes to dystocia during labor because it will cause anomalies of contraction. The interventions should not be avoided by the obstetrician if he is familiar with the fundamental surgical techniques, because no abortion has occurred in the author's cases and the labors were spontaneous and normal.

J. P. GREENHILL.

Leon, Juan: Prophylaxis of Dystocia Through Feto-Maternal Disproportion, *Rev. de ginec. e d'obst.* 38: 150, 1944.

The author discusses the usual well-known measures taken in disproportion cases due to contracted maternal pelvis. To reduce the volume of the fetus, two courses

have been recommended: first, Prochownik's diet which, by severe quantitative and qualitative restrictions of solid and fluid foods, is supposed to impede the growth of the fetus and to delay ossification of the head, and second, induced premature labor. The first is to be rejected because it produces serious disturbances in the pregnant woman and increases prenatal, natal, and neonatal mortality. In the second, the danger presented by the birth of too large a fetus can be avoided by roentgen studies of pregnancy.

Artificial premature labor can be carried out by drugs of recognized oxytocic action, calcium, quinine, and estrogens with quinine or extract of the posterior lobe of the hypophysis. But the best method, which can be used from the third month on, seems to be that of Aburel. It consists of making an intraovular injection by the transabdominal route of a 35 per cent solution of sodium chloride. To start labor during the last third of pregnancy or at term in the presence of a living fetus, the dose is 40 c.c.; if the fetus is dead, 80 c.c. The danger of causing intestinal or vesical lesions is easily avoided.

The author has used the Aburel method principally in women with serious chronic nephritis, pyelonephritis or toxemia, especially in pregnancies of over seven months, because the child is born alive with this procedure. But to avoid the objections that have been raised against other methods, it is imperative to establish the exact moment at which the procedure can be used without danger for mother and child, i.e., without exposing the mother to the danger of dystocia and the child to the danger of dying because of insufficient development.

Successful use of the method requires that the position of the fetus be carefully diagnosed and that the puncture be made in the midline between the umbilicus and pubis, not so high as to strike the placenta nor so low to the symphysis as to strike the fetal head. It is preferable to direct the needle toward the back or the anterior shoulder of the fetus. To avoid injecting the solution into the tissues of the fetus, amniotic fluid must be aspirated from time to time to make sure that the needle is in the cavity.

J. P. GREENHILL.

Puerperium

Aviles, Manuel: Surgery in Puerperal Sepsis, Rev. méd. de Chile 72: 388, 1944.

The author states that of 734 admissions for septic abortion during the past year, 616 had retention of septic remnants. In 443, early curetting followed by sulfonamide treatment was used, while conservative treatment was adopted in 173. Of the latter, 123 were subsequently curetted; 138 recovered satisfactorily, while 35 developed complications from which 10 died. Most of 443 patients convalesced satisfactorily; 54 developed complications, 15 of which were grave, resulting fatally in 7.

The results seem to contraindicate conservatism, but the patients treated in this manner were those admitted in serious condition with local or general inflammatory complications which contraindicate any other therapeutic method. In septicemia due to *Bacillus perfringens*, early curettage is imperative.

During the past eleven years, 20 hysterectomies were performed in patients with diffuse peritonitis: 14 died. In 178 patients with late hemorrhage in the course of a serious febrile puerperium, 14 hysterectomies were performed: 7 recovered, 3 died of acute anemia, and 3 of previous spread of the sepsis to the adnexae and blood. In 58 cases of perforation in septic abortion, 7 hysterectomies were performed: 4 healed rapidly, and 2 of the remaining 3 who had peritoneal infection died. The abdominal route is the one of choice for extirpation of the septic uterus.

Among 147 laparotomies for peritonitis, 20 required or were combined with extirpation of the uterus, 39 required extirpation of one or both adnexae, and in the remainder the surgery was limited to exploration and drainage until 1940, when the use of local sulfonamide therapy was instituted and contributed greatly to the success of the intervention. From 1940 to 1942, the mortality rate dropped from 87.5 per cent to 50 and finally to 35.40 per cent.

J. P. GREENHILL.

Bierer, Gideon: Post Eclamptic Kyphosis, J. Obst. & Gynaec. Brit. Emp. 51: 130, 1944.

The author reports three cases of kyphosis following eclamptic seizures. Two of these cases showed changes of the dorsal region similar to those described after tetanus and convulsive therapy. The third showed a traumatic disc rupture with compression fracture of the first lumbar vertebra. It is recommended that examinations of the spine be made in all cases of eclampsia before they leave the hospital and again in fourteen weeks. If spinal changes are present, a plaster of Paris cast should be applied for about twelve weeks.

WILLIAM BERMAN.

Perez, M. L., and Blanchard, O.: Local Intrauterine Sulfonamide Therapy as Prophylaxis in Puerperal Sepsis, Obst. y ginec. latino-am. 2: 165, 1944.

The authors used sulfanilamide locally in the uterus as a prophylactic procedure in Buenos Aires. They chose this route because of the local bacteriostatic action of the drug and because of the ready absorption from the uterus into the blood stream as proved by blood determinations. Furthermore, when oral or parenteral routes are used for the sulfonamides, larger doses are necessary to obtain satisfactory blood levels and this is not always without harm. Sulfonamido-chrysodine powder was used because, in addition to the other qualities of sulfonamides, it is hemostatic. The powder is instilled into the uterus a few hours after an obstetric operation by means of a special instrument. Among eighty women treated in this way only four had a slight fever (5 per cent). Among 131 women who were not given sulfonamides during the same period, the incidence of fever was 50.4 per cent. There was no instance of fever in all the cases of manual removal of the placenta treated prophylactically by the sulfonamides.

J. P. GREENHILL.

Contraception, Fertility, etc.

Staffs of Exeter, Barnstaple and Totnes Clinics of the Family Planning Assn.: Treatment of Involuntary Sterility, Lancet 246: 766, 1944.

The Eugenics Society of England, in its May meeting, 1944, discussed how the treatment of involuntary sterility has developed at the Exeter, Barnstaple and Totnes clinics of the Family Planning Association.

The first birth-control clinic in Exeter was opened in 1930, with a grant from the City Health Authority. Medical advice was to be made available not only on contraception but *also on involuntary sterility*. The shift of emphasis on their program is illustrated in a statistical fact: in 1933, 99 per cent of patients came for contraceptive advice and 1 per cent for advice on sterility; in 1943, the corresponding percentages were 67 and 33. Since the inception of the first clinic, 1933, which emphasized the positive and negative aspects of family planning, there has been considerable expansion of the program. The facilities now include three clinics, three cooperating hospitals encouraging reciprocal relationships, and pharmaceutical firms for the supply of endocrine preparations. The investigations included potentiometric hydrogen ion readings, wet and stained vaginal smears, endometrial biopsies, tubal insufflations, uterosalpingograms, semen analyses with sperm counts, testicular biopsies, pregnancy tests, Rh studies, serologic evaluations for syphilis, and smears for gonococci.

Up to March, 1944, 339 women had been seen complaining of complete or relative barrenness. These patients (the subfertile group) were compared to 300 fertile women. The subfertile series averaged 62 months in marriage while the fertile group averaged 78 months in the married state. Two hundred sixty-four cases (68 per cent) of the subfertile group disclosed histories of no pregnancies before the first, in contrast to 35 cases (11.3 per cent) among the fertile groups. The subfertile group averaged 0.16 live birth per woman as compared to 2.4 live births for women in the fertile group while there were 0.38 miscarriages per woman in the subfertile group as compared to 0.26 per woman in the fertile series.

Findings do not suggest that the use of contraceptives induces sterility but rather that the superfertile woman makes somewhat unsuccessful efforts to control

fertility by their use. Of the 389 subfertile women treated, more than 100 are untraced. Of the rest, 135 have conceived on one occasion or more, with 74 live births (3 the result of artificial insemination) and 46 miscarriages or stillbirths; 29 are pregnant now (1 the result of artificial insemination).

Advocates of a truly balanced planned parenthood program should become familiar with the interesting and succinet results of these clinics.

C. E. FOLSOME.

Israel, S. E.: *The Scope of Artificial Impregnation in the Barren Marriage*, *Am. J. M. Sc.* 202: 92, 1941.

In discussing the legal and moral aspects of artificial impregnation, the author calls attention to the fact that extreme care must be exercised in selecting the cases for insemination, and, in the event that the procedure is successful, in safeguarding the infant. Legally, he believes that written consent from both husband and wife, to which the husband has added that the child is his and his legal heir, is sufficient. Morally, the physician must be sure that both partners are in earnest and that no difficulties will arise in the future which may result in marital discord.

Technique consists in the introduction of semen from a healthy donor into the vagina rather than the cervix of the female at different periods in the cycle, as close as possible to the time when ovulation is assumed to occur. The necessity for repeated insemination is stressed, and six successful cases are presented.

FRANK SPIELMAN.

Pineda, R.: *Indications for Kymography and Hysterosalpingography*, *An. Cáted. clín. ginec.* 2: 208, 1943.

The author believes that in the diagnosis of tubal patency in the study of sterility, kymography should always be the first procedure. It is the most rapid, harmless, simple, and economical method for determining the permeability of the tubes. Hysterosalpingography is a more complicated and potentially harmful method, and should be used to complement other gynecologic procedures in the study of sterility.

The determination of the site of tubal obstruction is important both prognostically and surgically. The effect of successive insufflations always is to be preferred to application of hysterosalpingography for the purpose of eliminating tubal obstruction.

J. P. GREENHILL.

Pineda, R.: *Tubal Insufflation in Treatment of Dysmenorrhea*, *An. Cáted. clín. ginec.* 2: 205, 1943.

In a series of patients in whom tubal insufflation was done for sterility, the author discovered that a large proportion of them had had relief from menstrual symptoms after the first or second kyographic treatment. In a group of 350 patients who had insufflations, 45 per cent had suffered from dysmenorrhea, and of this number, more than half were relieved.

It is difficult to explain the mechanism of this effect, because the patients usually benefited are those who display no abnormality of the sexual organs, and have no history of infection or other lesions, and in whom the test for tubal patency is positive with normal pressure. In other cases it might be explained on the basis of removal of particles obstructing the tubes, or of increasing the lumen of the tubes or of dilating the uterine cavity. However, in patients who have bilateral obstruction in the uterine ends of the tubes, improvement in menstrual symptoms almost never occurs following insufflation. Other patients who are not benefited include those who are neuropathic and excitable; these may even have increased pain after kymography.

J. P. GREENHILL.

Anatomy, Anomalies, etc.

Evans, Mervyn W.: Congenital Dental Defects in Infants Subsequent to Maternal Rubella During Pregnancy, M. J. Australia 2: 225, 1944.

The author examined a number of children born to mothers who had rubella during pregnancy. These children were examined with reference to such dental defects as (a) variation in the number of teeth from normal, (b) hypoplasia, (c) abnormal tooth form, (d) restricted arch formation, (e) dental caries, and (f) gingivitis. Thirty-four babies were found whose mothers suffered from German measles during pregnancy. Of these 34 cases, 23 exhibited dental abnormalities. Sixteen of these 23 subjects exhibited retardation of eruption, and, with three exceptions, all of the 16 subjects showing retarded eruption were children whose mothers had suffered from rubella during the first two months of pregnancy. Hypoplasia was found in 8 instances. Evidence of defective tooth form was present in 7 infants. In 6 of the 34 infants whose mothers had suffered from German measles there was restriction in jaw development. This does not differ significantly from the normal. Four infants showed dental caries. Two of the infants showed gingivitis.

Examination of the results showed that as far as dental defects were concerned, the greatest deviations from normal were found in babies whose mothers contracted German measles during the sixth to the ninth week of pregnancy. The most striking abnormality was retardation of eruption. It is felt that rubella may act upon the dental primordia producing this disturbance.

WILLIAM BERMAN.

Anesthesia, Analgesia

Peralta Ramos, Alberto, Pelaez De Biondini, Paulina, and Labella De Bilbao, Maria Elena: The First Fifty Cases of Continuous Spinal Analgesia in Labor, Bol. Soc. Chilena de obst. y ginec. 23: 27, 1944.

The authors state that the method constitutes progress in obstetrics, but that it is not free from danger when used by a personnel without good training and foresight. Its application cannot be general and it fails in about 10 per cent of the cases in which it is used. Failure depends nearly always on obesity and especially on anomalies of the birth canal.

When used correctly, the method has no unfavorable effect on mother or fetus. The dilatation period is usually shortened because of the nervous block of the lower uterine segment and the cervix, while the expulsion period may be prolonged because of the block of the soft tissues. But this drawback can be eliminated by the efforts of the patient, by Kristeller's expression, or by forceps application.

At present, metycaine is probably the best anesthetic agent because of its lower toxicity, rapid effect, longer duration, and diffusibility. Unfortunately, its high cost makes it unavailable in hospital practice.

J. P. GREENHILL

Breasts

Brougher, John C.: Prevention and Treatment of Postpartum Fissured Nipples With Local Applications of Vitamin A and D Ointment, West. J. Surg. 52: 520, 1944.

Fissured nipples occur in 20.9 per cent of postpartum patients. Many ointments have been recommended for the prevention and cure of this annoying and potentially dangerous puerperal complication. Following the report of Weissberg, the author treated 200 cases of fissured nipples with local applications of vitamins A and D. Observations on these patients clearly indicate that vitamin A and D ointment is curative for the fissured nipple and an excellent prophylaxis for the puerperal breasts.

WILLIAM BICKERS.

Items

American Board of Obstetrics and Gynecology, Inc.

The following diplomates have been certified and are added to the previously published list: Dr. A. Franklin McCauley, 3047 St. Paul Street, Baltimore, Maryland; Lt. Ralph C. Benson, (MC) USN, U. S. Naval Dispensary, Federal Building, Long Beach 2, California.

Examinations

The next written examination and review of case histories (Part I) for candidates will be held in various cities of the United States and Canada and by special arrangements at Army and Navy Stations on Saturday, February 2, 1946, at 2:00 P.M. Candidates who successfully complete the Part I examination proceed automatically to the Part II examination held later in the year. All applications for this year's examinations must be in the office of the Secretary by November 1, 1945.

Arrangements will be made so far as is possible for candidates in military service to take the Part I examination (written paper and submission of case records) at their places of duty, the written examination to be proctored by the Commanding Officer (medical) or by a Medical Officer designated by him. Material for the written examination will be sent to the proctor several weeks in advance of the examination date. Candidates in military service who wish to do so may send their case records in advance of the examination date to the office of the Secretary. All other candidates should present their case records to the examiner at the time and place of taking the written examination.

The place of the Board's Part II examination in May or June, 1946, has not yet been decided, but it is likely to be held in that city nearest to the largest group of candidates. The exact time and place will be announced later.

If a candidate in Service finds it impossible to proceed with the examinations of the Board, so that his plans are thus interrupted, deferment of parts of these without time penalty will be granted under a waiver of our published regulations covering civilian candidates.

For further information and application blanks, address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh 6, Pennsylvania.

PAUL TITUS, M.D.

Philadelphia Committee for the Study of Pelvic Cancer*

It has been known for many years that, until the cause and a cure for pelvic cancer are discovered, the earlier the diagnosis is made and the sooner adequate therapy is instituted, the better is the chance of "cure." In view of this knowledge extensive study has been carried on to analyze the specific reasons for delay in making diagnosis or in instituting therapy. In the light of these studies the term "delay period" has been given to that period in the life of a cancer patient beginning with the onset of symptoms and ending with an established diagnosis and the institution of adequate therapy. Generally speaking, one of three factors is involved in any case where the "delay period" is prolonged: the physician, the patient, and the physician and the patient combined.

The physician has been responsible for a prolonged "delay period" on the following counts: failure to make a diagnosis, wrong advice, wrong treatment, no treatment, and failure to adequately examine the patient.

The patient has been responsible because of: fear of operation, fear of going to a doctor, fear of having cancer, economic reasons, etc.

*The above has been received from the Department of Public Health of Philadelphia, and is published as an item of information.

Both factors are combined when both physician and patient are at fault.

To shorten the delay period much time and money has been spent on educating the public. This has been done through periodicals, cancer society lectures, the press, medical societies, etc. All advice given follows the same pattern: visit the doctor regularly, report the earliest symptom, undergo periodic examination. The educational program has been well worth while. The public is responding more and more. People are going for routine examinations. In fact, the public has been so well educated that they are becoming very conscious of the fact that the medical profession has not kept pace with the public in the matter of being "cancer conscious." The public is becoming sufficiently educated to know what constitutes adequate examination by a physician and, in certain instances of gross neglect, has made public its dissatisfaction.

Some steps forward have been made by the medical profession to enable the public to obtain adequate medical examination and advice if and when they desire it. Cancer detection clinics have been established where periodic examinations can be made for the early evidence of cancer. These clinics are becoming more numerous, and are staffed by persons who are interested in the early diagnosis and treatment of cancer. When the educated public and these well-staffed clinics come in contact with each other there is no "delay period" and pelvic cancer no longer remains the terrible disease it is when neglected.

These clinics have not yet reached a majority of the people by any means, and the best approach still is through the practicing physician or family doctor. The latter must be educated in the latest advances in the diagnosis and the treatment of cancer. He must be made cancer-conscious almost to the point of assuming that a patient has cancer until proven otherwise. He must be taught to make detailed and careful physical examinations with adequate lighting and instruments and to obtain early biopsy in suspicious cases, with rapid referral of the patient to adequate therapy facilities. The responsibility for shortening the delay period is in the hands of the practicing physician, the family physician who sees the patient first and on whom the patient depends for advice and treatment.

In the light of these facts the Philadelphia Obstetrical Society has formed a committee for the study of pelvic cancer, the primary aim of which is the detailed study of the "delay period" in every case of death from pelvic cancer. The plan has the approval and cooperation of the Philadelphia County Medical Society and the Philadelphia Department of Public Health.

This committee will investigate in detail every death from pelvic cancer occurring in Philadelphia. The investigator will make a special study of that period of the patient's history from the onset of symptoms until adequate therapy has been instituted, the so-called "delay period." An attempt will be made in each case to explain the definite reason for any "delay" and to assign the responsibility to the patient, the doctor, the hospital, or to all, as the case may be.

The facts obtained from this study will be used as a means of educating the physicians of Philadelphia. The committee will meet each month to review the deaths of the previous month in an effort to decide from the facts where the blame for delay should be placed.

The data for these cases will be obtained from the physicians in charge of the case, from the hospital charts, and, when necessary, with the permission of the attending physician, from the relatives or the family of the patient. The data will be secured by a paid investigator of the committee who will personally call on the physicians, hospitals, etc.

As the work of this committee progresses and the monthly review of cases is carried on, the physicians in each case will be asked to take part in the discussion. Their presence at the discussion of their cases, and the presence of other interested physicians at these open meetings, will be a means of informing physicians of the work of the committee and of sensitizing them to the importance of keeping a "high index of suspicion" for pelvic cancer.

This committee is believed to be the first of its kind to be formed in this country. No previous attempt to "check up" on the physician and his handling of cancer cases has ever been done. The committee is patterned after the Philadelphia Maternal Welfare Committee, and hopes to accomplish for pelvic cancer what the Maternal Welfare Committee has accomplished in reducing maternal mortality in Philadelphia. It has high hopes that ultimately the Committee for the Study of Pelvic Cancer will be a comparable force in elevating the standard of care given to patients with pelvic cancer by the physicians of Philadelphia, and perhaps throughout the country, if similar committees are founded elsewhere.

The success of this committee depends on the obtaining of accurate and detailed information. This can be obtained for the most part only through the attending physician. His

cooperation and his willingness to give freely of his time and information is an essential need. The committee has been organized to work with and for the physicians of Philadelphia. It stands to further elevate the plane on which the practice of medicine in Philadelphia now rests.

The committee is financed by grants from the American Cancer Society and from the Philadelphia Obstetrical Society, which are barely sufficient to meet the present needs of the committee.

CLAYTON T. BEECHAM, M.D.

LEIB J. GOLUB, M.D.

THADDEUS MONTGOMERY, M.D.

MYER SOLIS-COHEN, M.D.

ELIZABETH WAUGH, M.D.

PHILIP F. WILLIAMS, M.D.

JOHN Y. HOWSON, M.D., Chairman

GEORGE A. HAHN, M.D., Treasurer

Committee for the Study of Pelvic Cancer

Announcement

Twenty-Fifth Anniversary Issue

The editors and publishers of the JOURNAL are preparing a special number to commemorate the completion of a quarter of a century of uninterrupted publication. This will appear in December.

American Journal of Obstetrics and Gynecology

VOL. 50

DECEMBER, 1945

No. 6

Twenty-Fifth Anniversary

THE AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY 1920-1945

TWENTY-FIVE years ago, in October of 1920, the first issue of the JOURNAL appeared as the successor of a periodical founded in 1868, the "American Journal of Obstetrics and Diseases of Women and Children," which ceased publication in 1919 after a notable career.

The work of these two journals together has covered an uninterrupted period of seventy-seven years, during which the specialty of obstetrics and gynecology has been represented by a monthly periodical devoted exclusively to its interests. Seventy-seven years is a long time. In this period the specialty has become transformed. The diseases of children as covered in the former "Blue Journal" no longer come within the domain of the doctor who confined their mothers. Moreover, the distinction between the gynecologist and the obstetrician is gradually disappearing and a great single branch of medicine has developed, formed from this fusion. The mechanical and surgical procedures, so important in the earlier history of obstetrics and gynecology, have become somewhat standardized, and the new interests of the specialty stem especially from the physiologic problems of the reproductive process.

During this past quarter of a century, medicine has participated in the revolutionary changes which have affected the entire world. We have seen, above all, the effort to make medical advances more available to all of the people, with a resulting expansion of governmental direction and control. The extension of direct medical service to a certain group of the people, as exemplified by the Emergency Maternity and Infant Care program, may be but the first of a succession of projects by which maternity care finally is to be provided through governmental funds for any woman who requests it. It is understandable that the fields of obstetric and pediatric practice should be the first to receive such attention, for there is a sentimental factor involved in caring for the Nation's mothers and children. These special fields may, however, serve simply as an area in which such measures are the first to be tried, and serve as a forerunner,

perhaps, of the extension of government activity in other branches of medicine. Whether such expansion from previous accepted methods will prove either desirable or beneficial is for the future to decide. There remains a lingering doubt in the minds of many physicians whether such measures, centrally controlled in the final analysis by a bureaucratic administration in the national capitol and supported by universal taxation, will bring about that practical ideal in maternal and infant welfare which we all desire.

In these last two and one-half decades of great social, political, economic, and scientific developments, medicine has occupied a leading role. Within the domain of the specialty embraced by the JOURNAL, signal advances may be recorded. Knowledge of the physiology of reproduction has advanced greatly, with the attainment in particular of a knowledge of the role of the endocrines, the morphologic development of the embryo, and the control of uterine contractility. Gynecologic and obstetric pathology has become an essential part of the personal knowledge of each practitioner of the specialty. The widespread use of blood and plasma has completely altered the outlook in major surgical operations and in obstetric hemorrhage. The sulfonamides and penicillin have revolutionized the treatment of infections. Radiation has been further developed in the treatment of cancer. Finally, the enlistment of the efforts of the practitioner of obstetrics in a great cooperative study has produced a phenomenal improvement in obstetric mortality and morbidity.

Of interest is the fact that the mechanical phases of gynecologic treatment show little change while the development of medical and physical methods of therapy and diagnosis has assumed such great prominence. While operative technics have been developed and expanded, the scalpel today is less in evidence than the test tube, the experimental and the research laboratory.

The JOURNAL has endeavored to keep pace with these developments. Its pages have reflected the progress of the specialty throughout our country and we feel that it has functioned satisfactorily as an organ for the dissemination of the new developments in its field. We are proud of this record and proud likewise to acknowledge the faith which our contributors and subscribers have had in the JOURNAL. The catholicity of its contents and the number of its readers are attested by the quoted references from its articles which have permeated American and foreign medical literature.

At the close of a quarter century of personal service to the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY, I want to commend the efficiency, liberality, and courtesy of our publishers, The C. V. Mosby Company. I am also proud to give recognition to the helpfulness and faithfulness of my associates, the late and lamented Dr. Hugo Ehrenfest, and Drs. Howard C. Taylor, Jr., and William J. Dieckmann, my immediate co-workers. Appreciation is likewise due to Dr. Robert T. Frank, the Editor of the Book Review Department, and to the staff of abstracters who have so efficiently recorded the world's literature in this field. To the members of the Publication Committee and to the Advisory Editorial Board an acknowledgment is also extended for their ever-ready co-operation.

George W. Kosmak, M.D.

THE PATHOGENESIS OF POSTSALPINGECTOMY ENDOMETRIOSIS IN LAPAROTOMY SCARS

JOHN A. SAMPSON, M.D., ALBANY, N. Y.

(From the Gynecologic and Pathologic Departments of the Albany Hospital and the Albany Medical College)

THE pathogenesis of endometriosis in laparotomy scars is not the same in all cases and its positive solution in a given case may be difficult or even impossible. It depends greatly on the type of the original operation and the anatomic conditions or relations resulting from it.

The progress already made toward a better understanding of the pathogenesis of scar endometriosis as well as the need for further studies are shown in the following brief historical review of this subject.

The first recorded case of endometriosis in a laparotomy scar was published by Meyer¹ in 1903. In keeping with observations made in the cases reported in the present paper, his case also followed salpingectomy and ventrofixation of the uterus. He believed that the endometriosis in his case arose from adenomatous changes in the uterine serosa in contact with the scar.

Von Franque² was the first to suggest that scar endometriosis might arise from the growth of bits of uterine mucosa transplanted into the abdominal wound. His case, reported in 1916, followed the repair of a perforation of the uterus caused by ovum forceps employed in the termination of an early pregnancy.

In the year 1926, Nicholson³ was able to collect only 28 cases from the literature. Fifteen of these followed ventrofixation of the uterus. He claimed that the continuity between the uterine mucosa and that of the growth in the laparotomy scar had not been established in a single instance in these cases and believed that the serosal theory offered the fewest difficulties in explaining the origin of the ectopic endometrial tissue.

In the year 1928, the writer⁴ reported two cases of endometriosis of abdominal scars following tubal sterilization and the extraperitoneal fixation of the fundus of the uterus in the abdominal wound. In both patients the uterus and the abdominal scar were removed at the second operation without disturbing the relation between the two. The microscopic study of sections, which included both the endometriosis of the scar and the portion of the uterus fused with it, in each case demonstrated that sprouts from the mucosa of one of the tubal stumps had invaded the uterine cornu and from there penetrated the abdominal scar. As far as I can ascertain, these are the first cases in which a continuity between normally situated Müllerian (tubal) mucosa and that in laparotomy scars has been reported.

In the year 1929, Hosoi and Meeker⁵ collected 87 cases. They presented a valuable abstract of these cases which were arranged chronologically. Thirty-seven of them followed ventrofixation of the uterus. They stated that "in those in which the fundus uteri was ad-

NOTE: The Editors accept no responsibility for the views and statements of authors as published in their "Original Communications."

herent to the tumor mass in the laparotomy scar, serial sections could demonstrate no endometrial tubules in the adherent portion of the uterus. This shows the laparotomy tumors in the literature were not due to an extension from the uterine cavity.' They also stated, "The transplantation theory seems to explain the majority of the cases, as most occurred after operation on the uterus and adnexa. The serosal metaplasia and the lymphatic theory have been applied to those instances in which a simple appendectomy has been performed and in which there was no hernia."

In the year 1930, Haselhorst and Otto⁶ reported 27 cases of endometriosis in laparotomy scars, 24 of which occurred after ventrofixation of the uterus. They believed that the endometriosis in all of these 24 cases was continuous with either the uterine or the tubal mucosa. In 14 cases they excised the tumor in the scar with the portion of the uterine wall adherent to it. By means of careful microscopic studies of this tissue they were able to demonstrate a continuity between the uterine or tubal mucosa and that in the endometriosis in the scar, frequently in the vicinity of silk threads employed in the fixation of the uterus. Their observations confirmed those which had been reported by me⁴ in 1928.

In the year 1930, two additional cases of scar endometriosis were reported by the writer.⁷ In the first one, the uterus, after both tubes and ovaries had been severed from their uterine attachments, had been drawn through the abdominal incision and its fundus fixed in the subcutaneous portion of the abdominal wall. At the last operation, twelve years later, the body of the uterus, together with a mass of indurated adipose tissue about each cornu, was removed and a ventrofixation of the cervix done. The uterine cavity was injected with gelatin containing graphite. In the microscopic study of the right cornu and the tissue about it, graphite was found in the lumina of Müllerian tubules in the tissue beyond the tubal stump. More sections demonstrated that tubules, which now contain graphite in their lumina, had actually sprouted from the traumatized tubal mucosa and had invaded the tissue about the stump. A similar study of the left uterine cornu was even more interesting. Normal healing of this tubal stump had occurred without any tubules from its mucosa growing out into the surrounding tissue, and graphite was not found in the lumina of the Müllerian tubules about it. It was inferred that the endometriosis about this stump, with a histologic structure similar to the preceding one, might have arisen from the growth of tubal mucosa transplanted in the wound at the time of the previous operation. The injection of the uterine cavity with graphite proved to be of the greatest value in ascertaining the pathogenesis of the endometriosis of the abdominal wall in this case.

In the second case the uterus had been fixed in the abdominal wound after removing both tubes and one ovary. At the last operation, four years later, the uterus and the laparotomy scar were removed. The uterine cavity was injected with gelatin containing bismuth subcarbonate. The specimen was studied in the same manner as the previous one. The scar endometriosis was fused with the center of the fundus and not with either uterine cornu, although stump endometriosis, in which the tubules contained gelatin, was present in both. Further evidence found in the study of this specimen indicated that the scar endometriosis had probably been derived from the uterine mucosa by continuous invasion in the attempted repair of a rent in the uterine wall probably caused by a ventrofixation suture which had penetrated the uterine cavity. Gelatin was not found in the scar endometriosis. When gelatin is present in cavities of scar endometriosis, we know they are continuous with the uterine cavity. When it is not found in any of these ectopic cavities, the origin of the scar endometriosis from the mucosa of a stump or fundus has not been positively excluded.

In the year 1934, Harbitz⁸ published an excellent monograph on scar endometriosis. He had collected from the literature 193 cases of endometriosis in laparotomy scars, of which 81 followed ventrofixation of the uterus, often combined with other operations on the pelvic organs. Only one of his own 15 cases followed ventrofixation of the uterus. In the remaining 14, two followed cearean section at term, and 12 hysterotomy for the termination of early pregnancy. He states that in Norway ventrofixation of the uterus is rarely employed, while hysterotomy for the termination of early pregnancy followed by tubal sterilization is a relatively common procedure.

In the year 1941, Wespi and Kletzhändler⁹ published a paper on cicatricial endometriosis. They commented on its rarity, stating that only 390 cases had been reported in the literature. Seventy-three instances of this condition had been encountered during the preceding sixteen years at the Zurich Clinic. Five of these followed cesarean section at term and 68 followed abdominal hysterotomy for the termination of early pregnancy. They believe that the transplantation of bits of uterine mucosa into the abdominal wound is the only possible explanation of the endometriosis in their cases. In support of this view, they report that since they have been employing a technique which, during the operation, lessens the soiling of the abdominal wound with the contents of the uterus, the incidence of scar endometriosis has been greatly reduced. With Harbitz, they believe that the endometrium of early pregnancy is more viable than that of pregnancy at term. Their observations have greatly strengthened the theory that bits of uterine mucosa transplanted in the abdominal wound may sometimes live and cause endometriosis in the scar. This phenomenon might easily have occurred in many of the reported cases which have followed other pelvic operations.

In the year 1942, Wyrens and Randall¹⁰ reported 31 cases of endometriosis in laparotomy scars occurring in the Mayo Clinic from the years 1916 to 1941. The preceding operations in these cases were: uterine suspension, 15; cesarean section, 4; salpingectomy, 4; hysterectomy, 2; myomectomy, 2; drainage of an appendical abscess, 1; appendectomy, 1; inguinal herniorrhaphy, 1; "pelvic operation," 1. "In 10 of the 31 cases the tumor in the abdominal wall was found to involve or was adherent to the uterus or tubes. Eight of these tumors involved the uterus alone; one was continuous with an endometriosis which involved the uterus and round ligament. In all but four of the 10 cases there was no evidence of a connection with the uterus or tubes. In four cases a connection with the lining of these organs was strongly suggested although not absolutely proved."

According to these authors, "the etiology of this condition is unknown but in most cases the best evidence points towards transplantation or invasion (migration) of endometrium from the lining of the uterus."

This review of the literature of endometriosis in laparotomy scars shows that not only has there been definite progress toward a better comprehension of its pathogenesis, but that there is also need for further studies. It has been shown positively that scar endometriosis can arise from normally situated uterine and tubal mucosa by continuous invasion. The very strong circumstantial evidence that it also arises from the transplantation of bits of uterine mucosa in the abdominal wound during hysterotomy for the termination of early pregnancy has greatly strengthened the possibility of the transplantation and growth of this mucosa in the abdominal wound during other pelvic operations.

A large number of these cases have followed salpingectomy or tubal sterilization combined with ventrofixation of the uterus. This type of operative procedure should create conditions favorable not only for the continuous invasion of the abdominal scar by tubal or uterine mucosa, but also for the growth of bits of these mucosae transplanted in this operative field.

From the year 1926 to the present time, 17 patients with laparotomy scar endometriosis have been encountered on the Gynecological Service of the Albany Hospital. This includes four cases previously reported by the writer.^{4, 7} Eleven of these patients had been operated upon primarily for conditions resulting from the injuries of childbirth: three for the sequelae of salpingitis; two for tubal pregnancy; and one for a uterine leiomyoma. In 16 patients the first operation consisted of bilateral salpingectomy or tubal sterilization followed by intentional or accidental ventrofixation of the uterus. Many of these patients

also had a preliminary uterine curettage and vaginal repair. In 10 of these 16 patients the fundus of the uterus was sutured extraperitoneally into the abdominal wound. In three patients an Olshausen type of operation, namely, ventrofixation by means of the suturing of both cornua to the abdominal wall, was performed. In all instances one or both ovaries were conserved. In one patient who had had bilateral salpingectomy for salpingitis without an inten-



Fig. 1.—Case 1. Photomicrograph ($\times 10$) of a frontal section through the left uterine cornu and a small portion of the postsalpingectomy scar endometriosis fused with it.

The patient, aged 31 years, para ii, complained of profuse and prolonged menstruation, incapacitating dysmenorrhea, and tenderness in her laparotomy scar during her menses. The latter symptom had been present for about a year. At her first operation in April, 1929, an "Olshausen ventrofixation" had been performed. "A knuckle of each tube was removed near the uterine cornu and the raw end of the cornu was sewed against the anterior abdominal wall." At the second operation, March 30, 1931, the scar endometriosis together with the uterus and the right tube and ovary were removed. The uterine cavity was injected with 15 per cent melted gelatin colored with lamplblack.

The mesial portion of the intramural part of the tube (the so-called "transitional zone") is well shown in this photomicrograph. At its left is the actual transition from uterine to tubal mucosa which is abrupt in this section. At its right is the lateral portion of the intramural part of the tube which forms the tubal stump. Note that gelatin, shrunken as a result of dehydration, is present in the lumen of the mesial portion of the tube and also in the glands of the mucosa lining the uterine cavity. It is even present in a gland, *a*, which has penetrated the myometrium. Only a little of the lateral portion of the intramural part of the tube appears in this section. It, too, contains gelatin, as does a lateral sprout or tubule, *b*, which has arisen from its mucosa and invaded the cornu, forming an endometriosis in this situation. Lateral sprouts originating in the mucosa of the intramural part of the tube may develop in the uterine cornua of women who have never had an operation. Even so, I believe that they may also arise from a tubal stump which has been pierced by a needle in the closing of the uterine cornu over it or as a result of the suturing of a cornu to the abdominal wall after salpingectomy, as in this case. Note the two gelatin-containing sprouts in the scar just above its fusion with the uterus. These will be discussed in the legend of the next photomicrograph.

tional suspension of the uterus, the left uterine cornu became connected with the laparotomy scar by the remains of a long persistent drainage tract. In only one patient in this series was salpingectomy not done. In this case the endometriosis followed the removal of an intramural myoma from the anterior wall of the uterine fundus. The first operation in ten of these 17 patients took place on the Gynecological Service of the Albany Hospital during the ten-year period from 1918 to 1927, inclusive, when bilateral salpingectomy or tubal sterilization, followed by ventrofixation of the uterus, had been performed 325 times. Since we have appreciated that this complication might follow this type of operation, it has rarely been employed.

The youngest patient was 28 years of age at the time of the second opera-



Fig. 2.—Case 1. Photomicrograph ($\times 10$) of a section similar to the preceding one and quite near it. To be more fully appreciated the two photomicrographs should be studied together. More of the scar and less of the cornu appear in this photomicrograph. Only a small part of the mesial or transitional portion of the tube and almost the entire length of the lateral portion are shown. Gelatin is present in the lumen of the lateral portion. Two gelatin-containing sprouts or tubules in the scar just above its fusion with the uterine cornu are shown in Figs. 1 and 2. The gelatin in their lumina indicates that they are continuous with the uterine cavity. From their situation one would infer that they were derived from the mucosa of the tubal stump. A study of other sections proves that the tubule at the right is definitely a terminal sprout from the mucosa of the end of the stump, while the tubule at the left appears to have been derived from a lateral sprout. The latter tubule, shown better in Fig. 1, is more definitely endometrial than the one at the right. Two large dilated tubules or cavities, lined by columnar epithelium and filled with old blood, are situated in the upper right portion of this section. A study of these two cavities in other sections suggests that they were probably derived from the two sprouts just described.

tion, and the oldest, 47 years; three were over forty. The shortest interval between the two operations was two years and the longest, seventeen. Symptoms referable to the scar endometriosis appeared in the majority of these patients in from one to three years after the first operation. However, two patients with extensive endometriosis did not have any symptoms referable to it until fifteen and sixteen years, respectively, after the first operation.

The pathogenesis of postsalpingectomy and posttubal sterilization endometriosis in laparotomy scars is but a further chapter in the complications resulting from the repair of salpingectomy wounds. In a previous study by the writer,⁷ tubal stumps from 100 patients who had had previous salpingectomy or tubal sterilization were carefully examined microscopically, many after injecting the uterine cavity with colored gelatin. As bilateral salpingectomy or



Fig. 3.—Case 1. Photomicrograph ($\times 10$) of a section from a part of the same block as the two preceding ones. Only a small portion of the cornu is shown. The scar endometriosis evidently had been torn in excising it. The tubular sprouts appearing in the two previous sections have invaded the scar more deeply. Gelatin is present in the tubules below the tear. A study of other sections from this general region strongly suggests that the endometriosis above the tear was continuous with that below it. The latter was derived from the mucosa of the tubal stump by continuous invasion. All the Mullerian mucosa in this portion of the scar endometriosis is definitely uterine in type. Yet the evidence is that this typical uterine mucosal tissue developed in the sprouts or tubules which grew out from the mucosa of the lateral portion of the intramural part of the tube. Was this portion of the tube lined by tubal or uterine mucosa? If the former, it must have been potentially endometrial. If the latter, it was abnormal for this portion of the intramural part of the tube. It is my belief that the endometrial type of tissue in the scar endometriosis actually arose from tubal mucosa which was potentially endometrial.

tubal sterilization had been done in 47 patients, a total of 147 stumps was available. Misplaced Müllerian mucosa was found in or about 112 stumps as compared with 16 instances of misplaced Müllerian mucosa in 200 cornua from 100 uteri, with intact tubes. Even in 50 uteri with intact tubes removed for the sequelae of salpingitis (a well-recognized cause of cornual endosalpingiosis), misplaced Müllerian mucosa was found in only 19 of the 100 uterine cornua. Therefore, preoperative endometriosis must be present in only a relatively small percentage of patients with tubal stumps. Postsalpingectomy endometriosis is but an evidence of the results of overactivity on the part of the tubal mucosa in the repair of salpingectomy wounds. It manifests itself by the outgrowth of sprouts, terminal or lateral, which arise from the mucosa of the tubal stump. These outgrowths in the form of tubules may invade not only the tissues about the stump, such as the uterine cornu in which the stump is frequently buried, but also any structure or organ such as intestine, ovary, or even the abdominal wall which may become adherent to this operative field.



Fig. 4.—Case 2. Frontal section through the fundus uteri and the postsalpingectomy scar endometriosis fused with the left cornu ($\times\frac{3}{4}$).

The patient, aged 37 years, para i, complained of severe dysmenorrhea and soreness in her laparotomy scar for the previous two years. This soreness was much greater during menstruation. She had been operated upon June 1, 1927, for prolapse of the uterus. At that time the uterus was curetted, the cervix amputated, pelvic floor repaired, appendix removed, both tubes severed close to the uterus and their cut ends buried in the cornua. The fundus of the uterus was then sutured extraperitoneally in the abdominal incision. At the second operation, Oct. 9, 1930, the scar endometriosis, which was fused with the left uterine cornu, was removed together with the uterus and both tubes and ovaries.

While distending the uterine cavity with gelatin colored with lampblack, some of the injection mass escaped from the left side of the scar endometriosis (see arrow). This phenomenon demonstrated that some of the endometriosis had been injured and possibly not removed. However, it was of much greater interest to me that Müllerian tubules and cavities in the scar must have been continuous with the uterine cavity. Endometriosis was present in both uterine cornua, but that in the right cornu, which arose from the mucosa of the distal stump of the tubal sterilization, had not invaded the laparotomy scar. A second and much smaller focus of endometriosis was present just below the first one in the subcutaneous portion of the scar. It was not adherent to the fundus of the uterus. It could have originated either as a part of the larger focus or as an independent process of transplantation origin.

One of the most interesting features of this misplaced Müllerian mucosa is that it may present both the structure and function of the uterine mucosa. This phenomenon may even occur in endometriosis arising from the mucosa of stumps of the isthmus of the tube. The tubal stumps in postsalpingectomy scar endometriosis have been situated in the intramural part of the tube in all the specimens which I have studied. Excellent descriptions of this part of the tube appear in papers by Schneider¹¹ and also by Geist and Goldberger.¹²



Fig. 5.—Case 2. Photomicrograph ($\times 5$) of a frontal section of the left uterine cornu and a portion of the scar endometriosis fused with it. A small portion of the uterine cavity and nearly all of the intramural part of the tube appear in this section. The intramural portion of the tube is lined by uterine mucosa and constitutes the tubal stump since the tube was severed close to the cornu. Shrunken bits of gelatin are present in the lumina of many of its endometrial glands. A magnifying glass is of great assistance in detecting the finer details of this tissue. To the right of the stump is an oval cavity, *a*, partially filled with the injection mass. It could be a distended portion of a tubule. Typical uterine mucosa with gelatin in the lumina of many of its glands occupies the upper portion of this cavity. This mucosa is continuous with similar mucosa in the cornu above and to the left of cavity *a*. To the left of this and above the end of the stump, is a narrow strip of uterine mucosa also with gelatin in the lumina of its glands. Other sections from this same general region demonstrate that these two ectopic foci of uterine mucosa with gelatin in their glands are continuous with each other and with the mucosa of the tubal stump. Therefore, they must have been derived from the latter by continuous invasion. In this section there is no indication of a continuity between the cornual endometriosis and that in the scar.

During the study of tubal stumps, endometriosis, which can be shown not to be continuous with the mucosa of the stump, is sometimes found in the operative field of the salpingectomy. Experimental salpingectomy was performed on uteri after their removal, in some of which the stump was purposely transfixed by a needle carrying a suture or otherwise traumatized. Microscopic studies of 48 of these uterine cornua showed bits of tubal mucosa embedded in 16 of them. If bits of tubal mucosa transplanted during salpingectomy grow in the immediate operative field, they should also sometimes grow in more remote fields, including the abdominal wound.

Frequently, a preliminary uterine curettage is done prior to a salpingectomy or tubal sterilization. During the manipulation of the uterus incident to

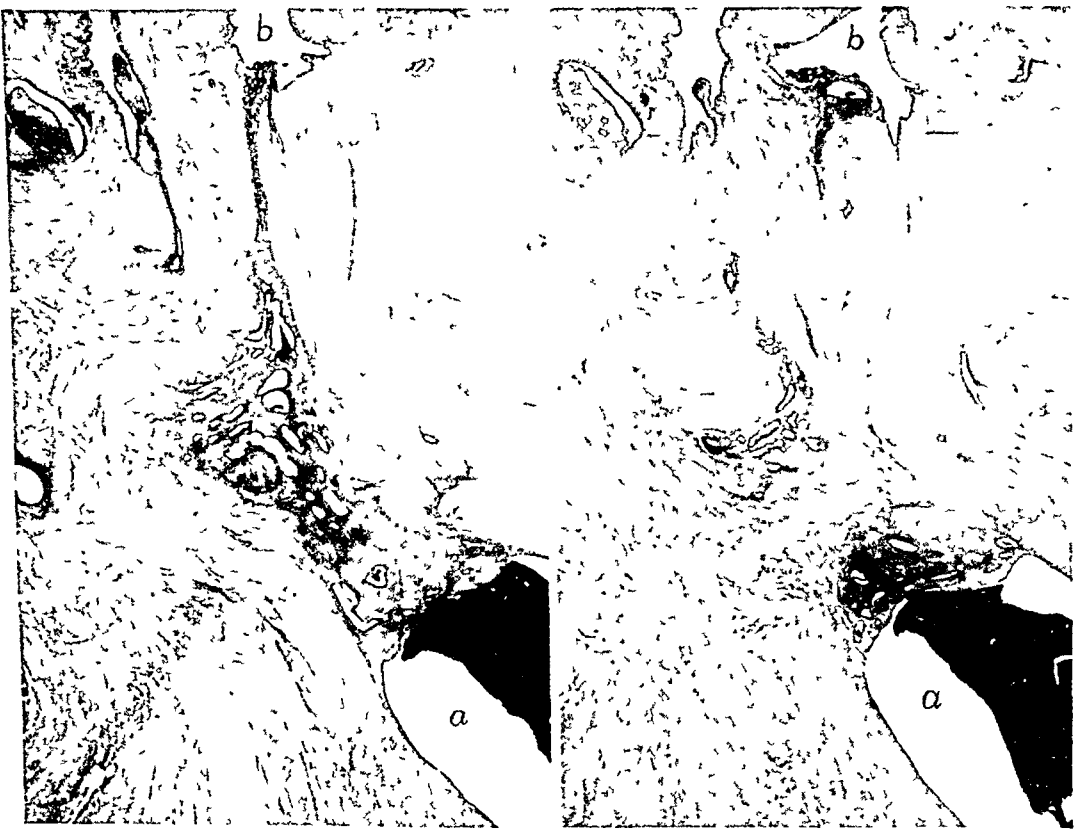


Fig. 6.—Case 2. Photomicrographs ($\times 8$) of two sections cut from the same block as the section shown in Fig. 5. These two photomicrographs should be studied together. The tubal stump no longer appears in either of these sections. However, the cavity labeled *a* is still present. It is lined by columnar epithelium which is continuous with that covering the endometrium in the upper portion of the cavity and also with that lining the glands which open on its surface. This uterine mucosa is likewise continuous with similar mucosa in the uterine cornu above cavity *a*. The latter mucosa has invaded the scar and appears to have invaded a small endometrial cavity or cyst, *b* (probably a dilated tubule). In the second section the lumina of some of the glands of the mucosa of this cavity contain gelatin, which can readily be detected with the help of a magnifying glass. This mucosa was derived from endometriosis in the cornu and the latter arose from the mucosa of the tubal stump, all by continuous invasion. The gelatin in these glands was injected into the uterine cavity and permeated their lumina as though they were lymph vessels. The presence of the injection mass in the lumina of these glands in the endometriosis of the cornu and the scar indicates that they are continuous with each other and with the lumen of the tubal stump and through it with the uterine cavity. The epithelium lining these glands is, therefore, continuous with that of the mucosa of the tubal stump and, through the latter, with the epithelium lining the uterine cavity.



Fig. 7.—Case 3. Photomicrograph ($\times 5$) of a frontal section through a postsalpingectomy scar endometriosis and a portion of the left uterine cornu fused with it.

The patient, aged 34 years, para ii, complained of pain in her laparotomy scar, worse after the cessation of her menstrual flow. She had been operated upon Sept. 11, 1926, for an adherent retroflexed uterus associated with a relaxed pelvic floor. The uterus was curetted, cervix amputated, and pelvic floor repaired. The left tube and ovary and the right tube were removed and the fundus of the uterus sutured extraperitoneally in the abdominal incision. The second operation was performed Sept. 21, 1932, when the uterus, together with the scar endometriosis fused with its left cornu, was removed.

The scar endometriosis contains many tubules, some small, others large. Some are lined entirely by columnar epithelium, others partly by epithelium and partly by uterine mucosa. Gelatin (shrunken as a result of dehydration) is present in many of them. Note especially the dilated tubule *a* and beneath it several smaller tubules (possibly all sections of the same tubule) each containing gelatin. The lumina of other tubules appear to be empty although some of the larger ones contain old blood. What is the origin of these tubules? I believe they arose as sprouts from the mucosal epithelium of the uterine cornu, shown at the left margin of the photomicrograph. This mucosa is in reality the mesial portion of the intramural part of the left tube and actually constitutes the tubal stump since the lateral portion of this part of the tube was excised by me at the first operation. Note that gelatin is present in the lumina of glands of the mucosa of the stump. Also note the small gelatin-containing tubule just above and to the right of the stump and its suggested continuity with the string of small tubules beneath dilated tubule *a*. The manner in which the tubules of the scar endometriosis arose from the mucosa of the tubal stump is shown in Fig. 8.

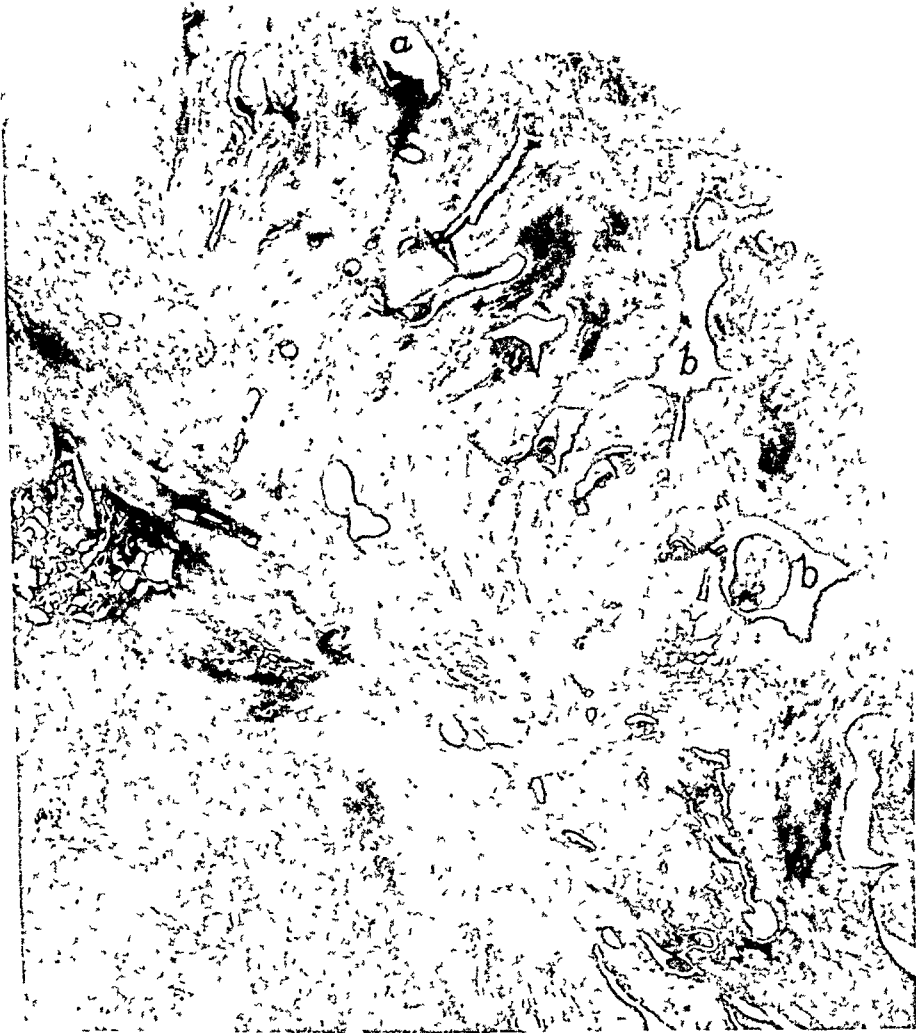


Fig. 8.—Case 3. Photomicrograph ($\times 5$) of a section from the same block as the preceding one and quite near it in the series.

The enlarged, distorted tubule marked *b* in Fig. 7, partially lined by uterine mucosa, including a polyp, appears in this section as two tubules separated by scar tissue. The dilated tubule *a* is smaller in this section than in the preceding one and a focus of uterine mucosa is present within it. Compare this with tubule *b* in Fig. 6 and note their great similarity. Note also the tubules beneath it which follow a course similar to those beneath tubule *a* in the preceding section. Like those, they are probably sections of the same tubule, the "stepping-stone" arrangement of which suggests that its course is very tortuous. Observe, too, the changes in the tubal stump. Its glandular tissue is now much nearer the scar than in the preceding section, is more distorted, larger, and more spread out, due to the fact that at least three sprouts have taken origin from it and invaded the uterine cornu about it. All of the gelatin-containing tubules shown in these two sections are not only continuous with each other but also with the glands in the mucosa of the tubal stump and through them with the uterine cavity. The continuity of all these lumina is clearly demonstrated by the presence of gelatin within them. The gelatin found its way out of the uterine cavity through tubules which arose from the mucosa of the tubal stump. *Tubules have, therefore, played just as important a role in the pathogenesis of the scar endometriosis in this case as glands did in the previous one.* What is the difference between Müllerian tubules and glands? Compare carefully the photomicrographs in the two cases. In the one case Müllerian tubules clothed in stroma formed the major part of the invading tissue; in the other, Müllerian tubules without appreciable stroma about them.

the salpingectomy, blood carrying bits of the uterine mucosa may escape through the uterine end of the severed tube (see Fig. 4 in previous paper⁴) and may be transplanted not only in the uterine cornu, but even in the peritoneal cavity or in the abdominal wound. Transplanted Müllerian mucosa has been held by many writers to be responsible for some of the endometriosis in laparotomy scars which followed salpingectomies.

The indications for the second operation varied greatly. The discomfort from the scar endometriosis was an important presenting symptom in 14 pa-



Fig. 9.—Case 4. Postsalpingectomy endometriosis of a laparotomy scar adherent to the left uterine cornu of a multinodular myomatous uterus ($\frac{3}{4}$).

The patient, aged 37 years and nulliparous, complained of profuse menses and severe dysmenorrhea during the previous two years. For the past year she also had had severe pain in the scar during menses, often associated with a discharge of blood from it at that time. The first operation occurred in the year 1920 when the appendix, both tubes and the left ovary were removed for "salpingitis" and both uterine cornua were sutured to the abdominal wall. At the second operation, July 10, 1936, the scar endometriosis together with the uterus and right ovary were removed.

Multiple uterine myomas and endometriosis in both uterine cornua are present. The endometriosis in the right cornu is confined to the uterus. It apparently arose from two sources, namely, the uterine mucosa of the cornu and the tubal mucosa of the stump. That which arose from the mucosa of the cornu is mainly uterine in type and that from the mucosa of the stump is tubal in type. The endometriosis in the left cornu is almost entirely of tubal type and is continuous with the endometriosis in the scar above and adherent to it. Note that symptoms referable to the scar endometriosis did not appear until nearly fifteen years after the first operation.

tients. Two of these had a bloody drainage from the scar during menstruation. Three of the patients also had uterine leiomyomas which caused menstrual disturbances. Symptoms referable to the scar endometriosis were pain and tenderness in the scar during menstruation which in some instances persisted after the cessation of the flow. The endometriosis was without symptoms in only two patients.

At the second operation the entire uterus, together with the portion of the laparotomy scar containing the endometriosis which was fused with or otherwise attached to the fundus uteri, was removed intact in 15 patients. In one patient who had had both tubes, one ovary, and a myoma removed twelve years before, a very extensive endometriosis of the abdominal wall developed, so massive that only a portion of it and the remaining ovary were removed.



Fig. 10.—Case 4. Photomicrograph ($\times 5$) of a horizontal section of the left uterine cornu, just below its attachment to the abdominal wall as shown in the preceding illustration. A cross section of the lumen of the mesial portion of the intramural part of the tube, which constitutes the tubal stump, appears at *a*. The lumen is partially lined by uterine mucosa and contains gelatin. Gelatin is also present in the tubule beneath it. The origin of this tubule, as a lateral sprout from the mucosa of the tube, can be seen in preceding sections, and in succeeding sections it can be shown that nearly normal healing of the end of the salpingectomy stump has occurred. Ectopic uterine mucosa does not appear in this section. The epithelial proliferation is all of tubal type, namely, endosalpingiosis, although the mucosa of the tubal stump from which it arose is partly lined by uterine mucosa. The injection of the tubules in this section is incomplete.

The specimens removed at operation were studied in the following manner: In 12 of them the uterine cavity was injected through the cervix with 15 per cent melted gelatin colored with some pigment, as in previous studies of the repair of tubal stumps. Lamp black proved to be very satisfactory. The remainder were not injected. Then the entire specimen, usually without incising the uterus, was chilled in ice water and hardened in 10 per cent formalin. Before or after fixation, sketches were made of it for future reference. The

"blocks" were so made that sections of the scar endometriosis and the portion of the uterus fused with it would show not only the relation between the ectopic Müllerian mucosa in the scar and any in the uterine wall, but likewise the origin of the latter from either the mucosa of the tubal stump or that of the uterus. The blocks were embedded in celloidin and many sections were cut.

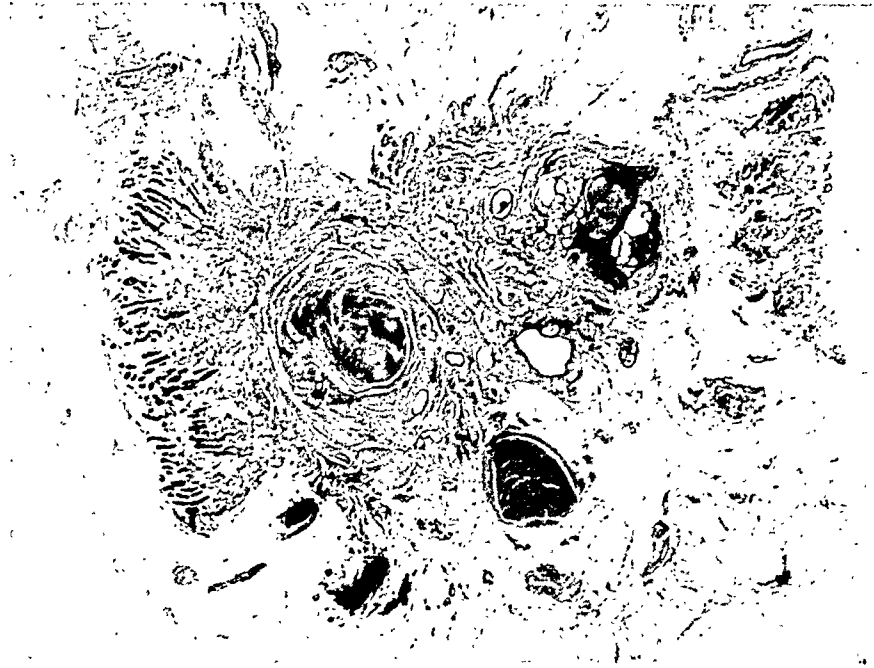


Fig. 11.—Case 4. Photomicrograph ($\times 5$) of a cross section of the scar endometriosis including some of the left rectus muscle. This section is taken about halfway between the section shown in the preceding illustration and the following one, and from the same series. Many tubules of varying sizes appear in cross section. Gelatin is evident in the lumina of only a few of these. However, its presence establishes the continuity of the lumina of these tubules with that of the intramural portion of the tube and through it with the uterine cavity. Uterine mucosa does not appear in the scar endometriosis in this section. It is occasionally encountered in some sections intermediate between this and those shown in the preceding and following figures. In these sections, however, the uterine mucosal tissue is relatively insignificant compared with that shown in Fig. 12.

Sections from many levels were always studied and in some situations serial sections were prepared. Even in noninjected specimens one may sometimes obtain a fairly accurate conception of the pathogenesis of the scar endometriosis. When one finds endometriosis of the uterine cornu which can be seen to have arisen from the mucosa of the tubal stump and when similar endometriosis is present in the scar fused with that cornu, the endometriosis in the two situations appearing to be continuous, one may justifiably conclude that the endometriosis in the scar probably is derived from the mucosa of the tubal stump by continuous invasion. In a specimen in which gelatin has been injected into the uterine cavity, if gelatin is detected in the lumina of tubules and other Müllerian cavities of a scar endometriosis, we have positive proof that these misplaced Müllerian cavities are continuous with the uterine cavity. The same telltale gelatin may enable one to ascertain the exact source of the scar endometriosis and the route taken by its mucosa in reaching the scar.

An example of the great value of this method of study was shown in a case of scar endometriosis in which the fundus uteri was not in actual contact with the abdominal wall at the close of the original operation but became connected with it by the remains of a drainage tract 7 cm. long. Gelatin injected through the uterine cavity was found in the scar endometriosis and also in endometriosis about the left tubal stump and in the entire length of the remains of the drainage tract. The latter was lined by columnar epithelium derived from the mucosa of the tubal stump. (See Case 5.)

In eight of the 12 specimens in which gelatin had been injected into the uterine cavity, gelatin was found in the lumina of some of the tubules and other ectopic Müllerian cavities of the scar endometriosis and also in the endometriosis about the end of the tubal stump. The exact source of the scar endometriosis in these cases was more easily and more convincingly demonstrated than in the specimens which had not been injected. In all of the eight specimens the scar

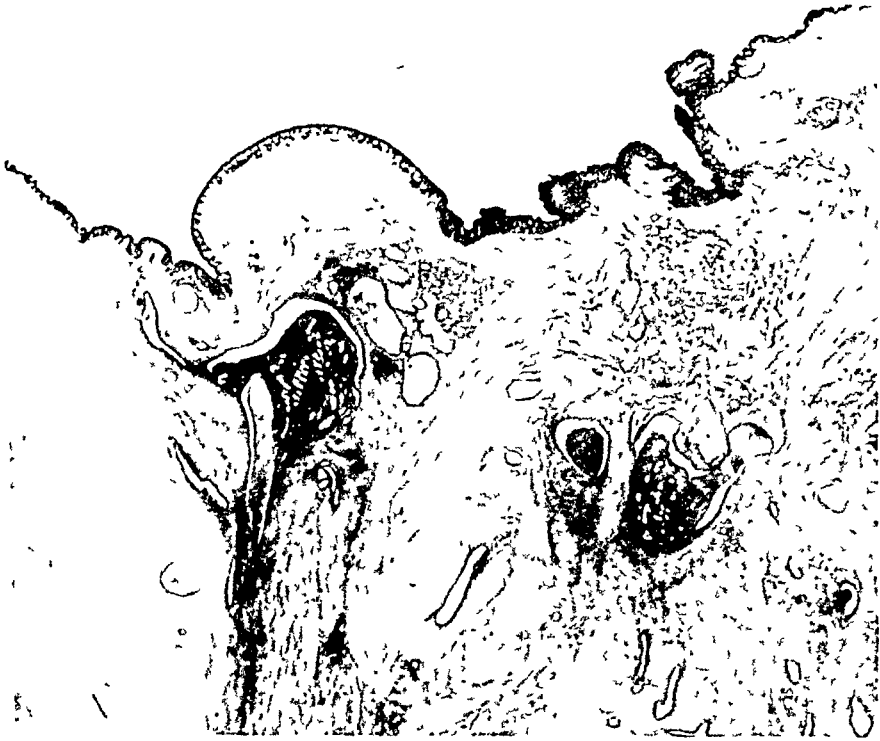


Fig. 12.—Case 4. Photomicrograph ($\times 5$) of a section of a portion of the scar endometriosis including the skin and subcutaneous tissues of the scar shown in Fig. 9 cut in a plane at a right angle to the preceding sections. Note the change in the Müllerian tissue. While tubules are present as in the preceding section, typical uterine mucosa is also present. There seems to be a very intimate relation between these two types of Müllerian structures as though typical uterine mucosa had arisen from the lining of the tubules. Gelatin is not found in the lumina of any of the tubules or of the glands of the uterine mucosa in this portion of the scar endometriosis. However, it is present in the lumina of tubules in sections from a block of the subcutaneous portion of the scar endometriosis adjacent to this one. In these sections very little mucosa of uterine type is seen.

The "spotted" injection of the lumina of tubules in scar endometriosis has its significance but is most tantalizing and also stimulating. What is the source of the typical uterine mucosa in this section? I believe that all of the Müllerian epithelium came from the mucosa of the tubules in the preceding sections, beginning with the one shown in Fig. 10. The source of the stroma, however, is more difficult to determine and presents an interesting problem.

endometriosis arose from the invasion of the abdominal wall by the mucosa of the tubal stump.

In each of the scars of two of these eight specimens, two distinct and separate foci of endometriosis were present. In the first case endometriosis had developed about each uterine cornu. In the tubular structures of one focus gelatin was found but it was not present in the other. The origin of the first focus was undoubtedly due to tubules from the mucosa of the end of the tubal stump which had invaded the tissues of the abdominal wall about the stump. In the second focus the endometriosis could have been of transplantation origin (see Case 2 in a previous paper⁷). The second case with two separate foci was

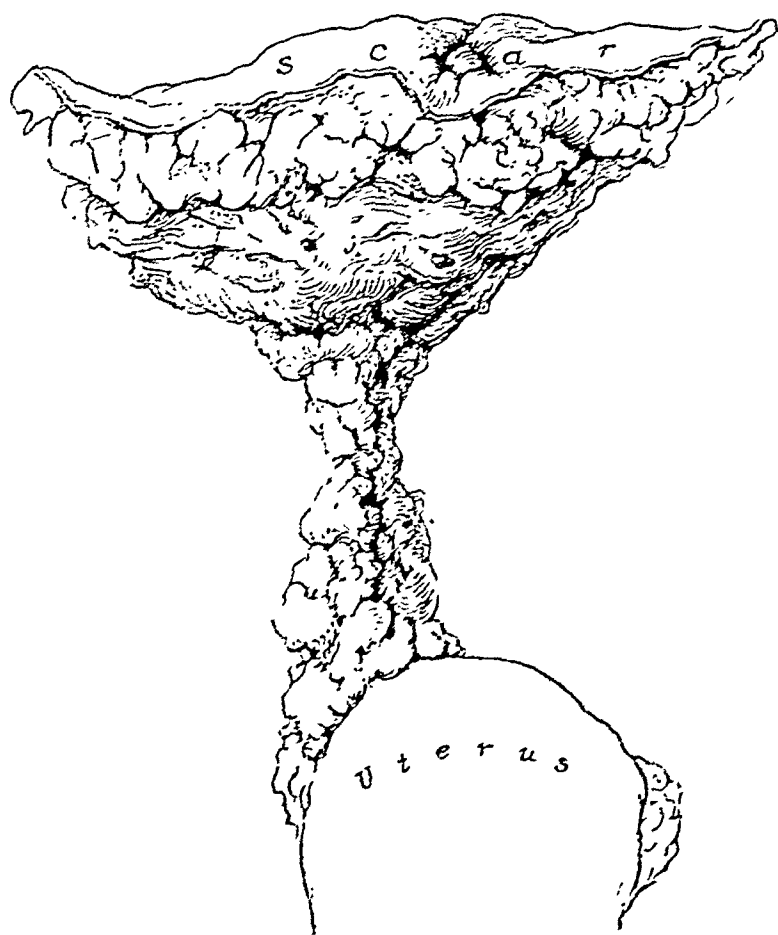


Fig. 13.—Case 5. Postsalpingectomy endometriosis of a laparotomy scar attached to the left uterine cornu by a drainage tract 7 cm. long ($\times \frac{3}{4}$).

The patient, aged 34 years, para iii, complained of severe pain in her laparotomy scar, especially during menstruation. She had first been operated upon on Feb. 21, 1928, when the appendix, both tubes, and the left ovary were removed for bilateral subacute salpingitis. The pelvis was drained through the abdominal incision by rubber tubes which were removed on the tenth postoperative day. A persistent drainage tract resulted which would "close and reopen with a bloody discharge at every menstrual period since the first one, ten weeks after the operation." At the second operation, Oct. 3, 1940, the scar endometriosis together with the uterus, right ovary, and remains of the long drainage tract were removed.

The uterine cavity was distended with lamphack-colored gelatin which was later found in the lumina of some of the tubules and cavities in the base of the scar endometriosis, thus demonstrating their continuity with the lumen of the drainage tract and through it with the tubal stump and the uterine cavity.

similar to the one just described in that gelatin was found in the scar endometriosis which was fused with one uterine cornu. It was not found, however, in the second focus which had no apparent connection with either the first focus or with the fundus of the uterus. The second focus of scar endometriosis could have been of transplantation origin.

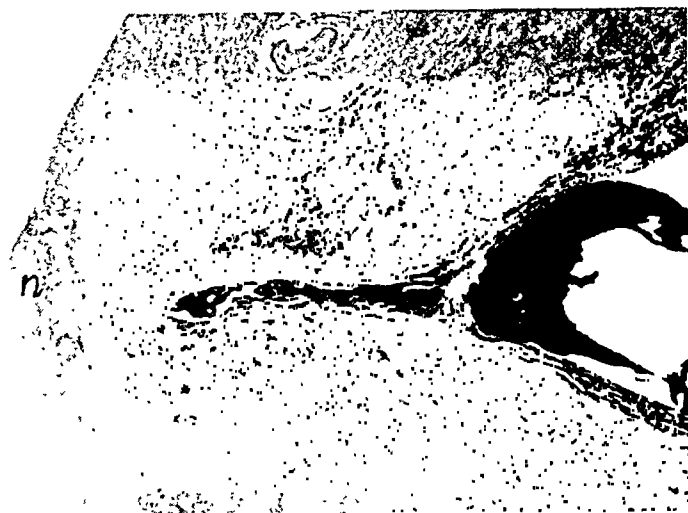


Fig. 14.—Case 5. Photomicrograph ($\times 5$) of a horizontal section of the right uterine cornu shown in Fig. 13. Some of the uterine cavity, all of the mesial and the beginning of the lateral portion of the intramural part of the tube, appear in this section. The remainder of the lateral portion appears in succeeding sections of this series, in which it is shown to end without either terminal or lateral sprouts in the small nubbin marked *n*. The transition between uterine and tubal mucosa occurs quite abruptly at the beginning of the mesial portion of the intramural part of the tube.

The absence of gelatin in the lumina of Müllerian tissue in a scar endometriosis does not always signify that the ectopic tissue had not arisen by continuous invasion from the mucosa of a tubal stump. When gelatin was found in the lumina of this tissue, it was usually in the lumina of tubules in the base of the scar endometriosis near the tubal stump. In only one of the eight specimens in which gelatin was found in the lumina of the tubules was it present in all parts of the scar endometriosis. Even in this case, however, it was not present in every tubule. (See Case 3.) Nevertheless, some of the most interesting observations were made in specimens with a limited injection of the scar endometriosis. (See Case 2.) The failure to obtain more complete injections must have been due either to actual obstruction of the lumina of the tubules which were partially injected or not injected at all, or to the employment of insufficient pressure when injecting the gelatin mass through the uterine cavity. Uterine mucosa frequently develops in the lining of these tubules. I am sure that this phenomenon was responsible for the failure, in at least some instances, of the injection mass to penetrate the endometriosis more extensively. I tried using greater pressure during the injection of the uterine cavity but this procedure only caused the extravasation of gelatin into the interstitial tissues of the endometrium, especially in the ectopic uterine mucosa.

We know that the intramural portion of the tube may be occluded in patients who have never been operated upon and may, therefore, be present be-

fore the first operation is performed. Such occlusion may also develop after the first operation, proximal to the incised end of the tubal stump and may have no relation to it. In these cases gelatin could not pass from the uterine cavity into any tubules which might arise from the end of the stump. Under these circumstances gelatin would not be found in the tubules of the scar endometriosis. Gelatin also would not be present in the tubules of a scar endometriosis of transplantation origin or in one resulting from the extension of a peritoneal endometriosis of the portion of the uterine fundus which became adherent to the scar.

In four of the 12 injected uteri, gelatin was not found in the scar endometriosis. In the first of these the scar was fused with the central portion of the

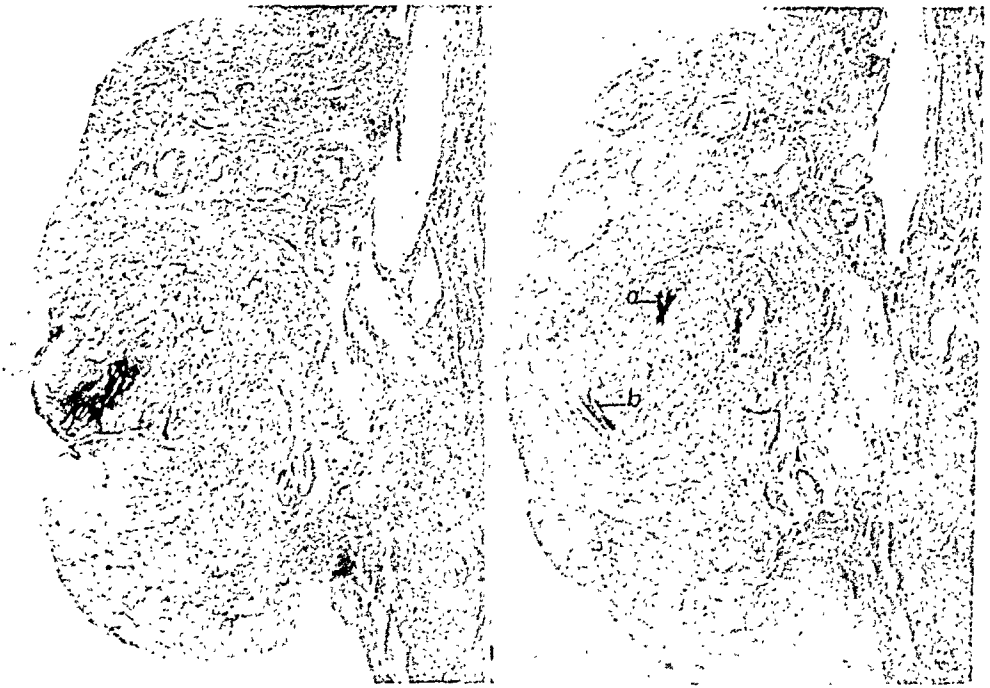


Fig. 15.—Case 5. Photomicrographs ($\times 8$) of two sections of the nubbin marked *n* in the preceding illustration and from the same series.

In the first section the endometriosis consists of glands and stroma similar to uterine mucosa. Mesial sections in the series show that, at present, this mucosa is not continuous with the mucosa of the tubal stump but is situated very near the end of the stump. The second photomicrograph is also of the same nubbin in a nearby mesial section. Here lampblack appears in a lumen *a* which resembles that of the isthmus of the tube but lacks an epithelial lining. However, mesial section show lumina continuous with this one, which contain lampblack and are lined by normal-appearing tubal mucosa. Below the end of the tubal stump *a* is a narrow space *b* lined by Müllerian-like tissue including its epithelium, but without lampblack in its lumen. This tissue is not continuous, now, with tubal mucosa mesial to it but is a part of the endometriosis shown in the first section.

This series of sections of the uterine cornu portrays the operative technique probably employed in removing the tube from the uterine cornu. They also show some of the results of the attempted repair of the damage (mutilation) inflicted upon the tubal stump during the operation, such as severing the tube, possibly clamping it, and, in this instance, strangulation by sutures. I believe that the endometriosis shown in the first photomicrograph arose from a bit of tubal mucosa which was "pinched off" or otherwise separated from the rest of the stump during the operation. A tightly tied suture could have done this very readily. I also believe that this bit of mucosa was originally of tubal type and has acquired the structure of uterine mucosa.

uterine fundus and the endometriosis was believed to have been derived from the mucosa lining the uterine cavity and not from the mucosa of a tubal stump.

In the second case, small foci of endometriosis were present in the scar fused with the right uterine cornu and also about the ends of the tubal stumps in both cornua. Gelatin was present in the lumina of both tubal stumps but not in the endometriosis about them or in the scar. This could have been caused by the occlusion of the lumina of the ends of the tubal stumps after development of the scar endometriosis.

The third case in which no gelatin was found in the endometriosis of the scar was most confusing. It presented the appearance of an endometriosis arising on the surface of the cornu and simultaneously invading the myometrium beneath it and the adjacent scar which was fused with the uterine wall. Peritoneal endometriosis, however, was not observed at the time of the first operation. Microscopic examination of the tissues about the tubal stump in this case was unsatisfactory.



Fig. 16.—Case 5. Photomicrograph ($\times 5$) of a horizontal section of the left uterine cornu and the scar fused with it at the base of the drainage tract shown in Fig. 13 and approximately at the same level as the section of the opposite cornu shown in Fig. 14. Nearly the entire intramural part of the tube is shown in this section. It constitutes the tubal stump because the tube had been removed close to the cornu. It is lined by typical uterine mucosa with gelatin in the lumina of its glands. The extravasation of gelatin into the distal portion of this mucosa marred this tissue and also permitted the escape of more gelatin into the drainage tract than otherwise would have occurred. However, in spite of this artefact, it is clear that the columnar epithelium lining the drainage tract was derived from the stump mucosa which had invaded its lumen before the uterus was removed. (See the next photomicrograph.)

There is a postoperative endometriosis in the scar, at the right, which is fused with the uterine cornu. Gelatin is present in its Müllerian tubules. These tubules arose as lateral sprouts from the mucosa of the stump and invaded the scar as laparotomy scars are invaded under similar conditions. (Compare with a similar section of the right cornu shown in Fig. 14.) Both cornua had the same operative treatment except that a persistent drainage tract was in contact with the left uterine cornu and not with the right. The entire intramural part of the right tube is lined with tubal mucosa while that of the left is lined with uterine mucosa. Direct endometriosis has arisen from the mucosa of the left tubal stump but not from that of the right stump.

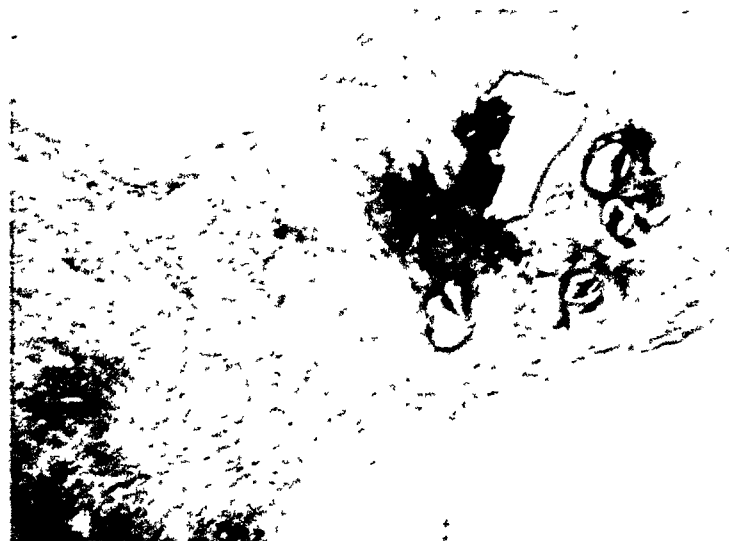


Fig. 14.—Case 5. Photomicrograph ($\times 5$) of a section of the uterine cornu and near endometrioid, shown in the pooling dissection, and from the same section, about 5 mm. above the latter.

Gelatin is present in the tubules and also in the larger "cavity" of the tract. This cavity is merely a cross section of the lumen of the lower portion of the former pelvic drainage tract which had extended through the abdominal incision. It is lined by columnar epithelium except for typical uterine mucosa, which occupies the portion of the "cavity" nearest the uterine cornu. The relation between the preceding illustration and this one demonstrates that the uterine mucosa shown here is continuous with that of the stump and that the latter has grown out through the end of the stump into the lumen of the tract. The columnar epithelium lining the tract must have been derived from this source.

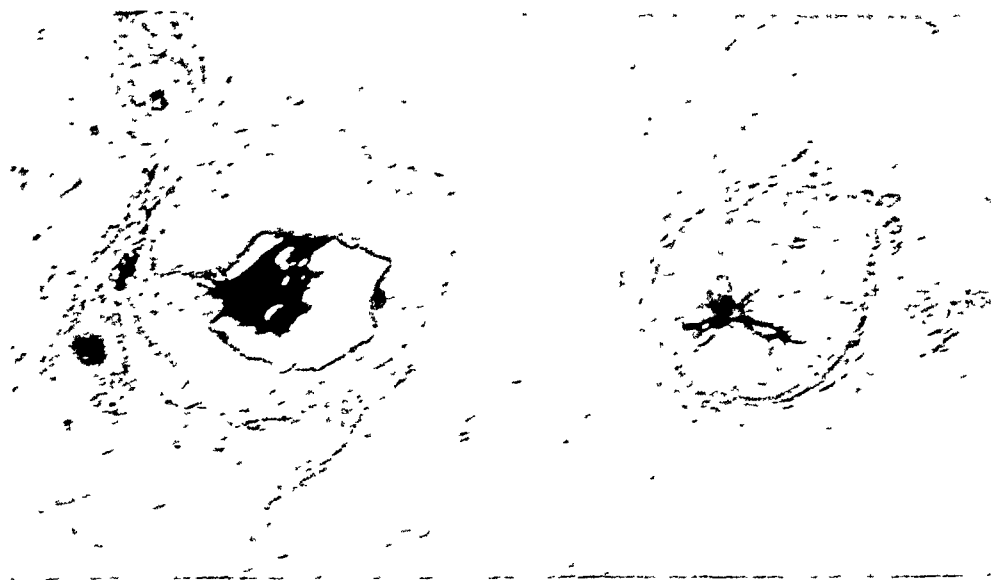


Fig. 15.—Case 5. Photomicrographs ($\times 5$) of two cross sections, taken at different levels, of the drainage tract shown in the preceding illustration. The first is from the lower portion of the tract above the last section and the second is from the upper portion, just below the section shown in the next illustration. The entire tract is lined by columnar epithelium which is continuous with the epithelium of the mucosa of the tubal stump and also with that of the Müllerian structure in the near endometrioid. The second section is from the narrowest portion of the tract.

In the fourth and last case, a preliminary uterine curettage, removal of the right tube and ovary for tubal pregnancy, and left tubal sterilization followed by ventrofixation of the uterus had been performed. The second operation, seventeen years later, was undertaken for dysmenorrhea and too frequent menstruation associated with pain and tenderness in the abdominal scar. The latter symptoms had been noticed for only a year. At the second operation, the scar endometriosis, fused with the right uterine cornu, was removed with the uterus. A small focus of endometriosis was found about the end of the tubal stump in each cornu. The endometrial tissue in the right cornu arose from the mucosa of the tubal stump and its tubules contained gelatin. A careful study of this cornu and the portion of the scar adherent to it failed to show any connection between the endometriosis of the cornu and that in the scar. It was judged that the scar endometriosis might have resulted from the transplantation of endometrial tissue. The preliminary uterine curettage at the first operation increased the possibility of such an origin.

In four of the 16 specimens from patients with bilateral salpingectomy or tubal sterilization, the uterine cavities were not injected. Two of the patients were operated upon before the method was employed. In both of these cases



Fig. 19.—Case 5. Photomicrograph ($\times 21\frac{1}{2}$) of a cross section through the central portion of the scar endometriosis shown in Fig. 13, and at a right angle to the preceding sections of the drainage tract. This section also includes the terminal portion of the intra-abdominal part of the drainage tract at the left and the skin covering the scar at the right. The portion of the tract shown here has again a relatively large lumen which becomes much smaller at the point, not shown in this illustration, where the tract enters the base of the scar. In the latter location many tubules arise from the tract and invade the scar in as many directions. As previously stated, the entire tract is lined by columnar epithelium continuous with that of the mucosa of the tubal stump. However, other sections in this series show that uterine mucosa, sometimes in polypoid form, has in places replaced the lining of the more proximal portion of the tract. Gelatin was found in the lumina of several tubules and even in the glands of typical uterine mucosa in the base of the scar endometriosis (not shown). One may thus conclude that at least all of these tubular structures were continuous with the lumen of the drainage tract and through it with the uterine cavity.

There is only one possible source of the Mullerian mucosa in this scar endometriosis, namely, the lining of the drainage tract, and the latter came from the mucosa of the tubal stump, all by continuous extension and invasion.

the scar endometriosis was fused with a uterine cornu in which endometriosis was present. These two cases have been previously reported⁴ and also mentioned in the present paper.

In a third case, the second operation was performed thirteen years after the previous one in which a myoma, both tubes, and one ovary had been removed, and both uterine cornua sutured to the abdominal wall. The scar endometriosis, fused with both uterine cornua, was so extensive that only a portion of it and the remaining ovary were removed.

In the fourth case, the last operation was performed ten years after the previous one. The scar and the fundus uteri were so badly mutilated in removing them that the uterine cavity was not injected. The portion of the scar adherent to the left uterine cornu contained a hemorrhagic cyst, 3.5 cm. in diameter and partially lined by columnar epithelium. Müllerian tubules were present both in the uterine cornu about the stump and in the fibrous tissue uniting the cornu with the tissue about the cyst. One would infer that the scar endometriosis was derived from the mucosa of the tubal stump by continuous invasion or transplantation.

Discussion

Seventeen cases of laparotomy scar endometriosis have been studied. The first operation, in all but one case, consisted of bilateral salpingectomy or tubal sterilization followed by intentional or accidental ventrofixation of the uterus. In the one case in which salpingectomy had not been done, the scar endometriosis followed a myomectomy. In all but one of the 16 postsalpingectomy cases, the scar, together with the uterus, was removed at the second operation. In that one case the endometriosis, apparently fused with both uterine cornua, was so extensive that only a portion of it and the remaining ovary were removed. In all but two of these 15 specimens the scar endometriosis was fused with a uterine cornu. In one of these two cases the fundus was not in actual contact with the wound at the close of the first operation but its left cornu became connected with the scar by the remains of a long drainage tract. In the other case the scar endometriosis was fused with the center of the fundus and not with either uterine cornu although stump endometriosis was present in both. In this case I believe that the scar endometriosis was derived from the mucosa of the fundus by continuous invasion in the attempted repair of an evident rent in the uterine wall, probably caused by a ventrofixation suture which had penetrated the uterine cavity.

Endometriosis was found about the tubal stumps in the 13 uterine cornua which were adherent to the scar endometriosis as well as in the cornu not in actual contact with the scar but connected with it by a long drainage tract. It was present about the tubal stumps in both cornua in 11 of these 14 uteri but in only one instance had the endometriosis in both cornua invaded the scar, thus causing two foci of endometriosis in it. In the remaining 10 cases, the scar endometriosis was derived from only one tubal stump and that about the other stump was confined to the cornu itself.

I was able to ascertain that the scar endometriosis was derived from the mucosa of a tubal stump by continuous invasion in 10 specimens. It probably arose in a similar manner in three others. In two additional specimens such an origin could not be excluded although one of these might have been of transplantation origin and the other secondary to a possible peritoneal endometriosis of the uterine cornu.

Transplantation endometriosis was possibly present in three scars. One of these is mentioned above. In the remaining two cases two separate foci of endometriosis were found in each scar, one of which was proved to have arisen by continuous invasion from the mucosa of a stump. The other possibly developed as a result of transplantation.

The postsalpingectomy scar endometriosis which I have studied has resulted from the outgrowth of terminal or lateral sprouts of the mucosa of the tubal stump. These, as tubules, invade the tissues about the stump, usually the uterine cornu. From here they spread to the portion of the laparotomy scar attached to that cornu.

Injecting the uterine cavity with colored gelatin, a method proved to be of great value in studying the pathogenesis of postsalpingectomy endometriosis in other situations, has also been very helpful in the study of these cases, in 12 of which the uterine cavity was injected. Gelatin was found in the scar endometriosis in eight of these, thus demonstrating the continuity of their tubules with the uterine cavity. The same "telltale" gelatin indicated the source of the endometriosis and the routes taken by sprouts from normally situated Müllerian mucosa in their invasion of the scar. The most dramatic demonstration of the great value of the injection method in ascertaining the pathogenesis of postsalpingectomy scar endometriosis was the presence of gelatin in the tubules of a scar in which the only contact with the uterus was the remains of a drainage tract 7 cm. long. This same specimen likewise showed the ability of Müllerian tissue to extend itself by continuous growth and invasion for a long distance. In this instance the mucosa of the left tubal stump had grown out through the end of the stump into the lumen of the drainage tract entirely lining it with columnar epithelium. The drainage tract ended, as such, at the base of the scar. Here sprouts had arisen from its mucosa and had invaded the scar actually to the skin epithelium. The total distance traveled by the continuous extension and invasion from the stump mucosa was 11 centimeters. (See Case 5.)

In four of the 12 injected specimens, the gelatin did not reach the scar endometriosis. The reason for this failure was judged to be a mechanical one in three instances and actual lack of continuity in the fourth where the endometriosis could have been of transplantation origin.

An alluring feature of postsalpingectomy endometriosis is that the ectopic mucosa, which can be shown to have had its origin in the mucosa of a tubal stump and to have grown from it by continuous invasion, may not only retain the structure of the tubal mucosa, thus being actually an endosalpingosis, but may also assume both *the structure and function of the uterine mucosa*,

including its reaction to menstruation and pregnancy, thus producing true endometriosis. Even the endometriosis derived from the stump of the isthmus of the tube may be of uterine type. In the summaries of two previous papers published by the writer in the years 1928 and 1930, respectively, this feature of tubal stump endometriosis was stressed.

Mucosa of uterine type was present in the scars of all specimens of post-salpingectomy scar endometriosis which I have studied. In some specimens the endometriosis of the uterine cornu, which was proved to have been derived from the mucosa of the intramural part of the tube, was definitely of tubal type. However, after these tubules had penetrated the scar, typical uterine mucosa appeared in and about them. (See Case 4.) In other specimens the entire intramural part of the tube, which constituted the stump, was lined by mucosa of uterine type. The endometriosis of the cornu which had arisen from this mucosa, and the scar endometriosis continuous with it, were of uterine type. (See Case 2.) In my previous studies I had observed only a few instances in which the tubal mucosa of a stump had been replaced by mucosa of uterine type which was described by me as activated tubal mucosa. (See Figs. 10, 13, 16, and 32 of a previous paper.⁴)

The most fascinating observation made in this study of postsalpingectomy scar endometriosis is the ease with which the gelatin, at times, flowed through the lumina of tubules and glands as though they were lymph vessels. In some specimens of scar endometriosis, tubules play the more prominent role and in others, glands; they are the leaders and life of the invasion. (Compare Cases 2 and 3.) A tubule is a Müllerian gland without appreciable stroma about it, and a gland is a Müllerian tubule clothed in stroma. Otherwise, Müllerian tubules and glands are essentially one and the same as far as the pathogenesis of post-salpingectomy endometriosis is concerned.

This work was done with the aid of the facilities afforded me in the Pathology Department of the Albany Medical College and the technical skill of Miss Helen Buchan.

References

1. Meyer, Robert: *Ztschr. f. Geburtsh. u. Gynäk.* 49: 32, 1903.
2. von Franqué, Otto: *Zentralbl. f. Gynäk.* 40: 953, 1916.
3. Nicholson, G. W.: *J. Obst. & Gynaec. Brit. Emp.* 33: 620, 1926.
4. Sampson, J. A.: *AM. J. OBST. & GYNEC.* 16: 461, 1928.
5. Hosoi, K., and Meeker, L. H.: *Arch. Surg.* 18: 63, 1929.
6. Haselhorst, G., and Otto, K.: *Ztschr. f. Geburtsh. u. Gynäk.* 98: 193, 1930.
7. Sampson, J. A.: *AM. J. OBST. & GYNEC.* 20: 443, 1930.
8. Harbitz, H. F.: *Acta chir. Scandinav. (Supp. 30)* 74: 1, 1934.
9. Wespi, H. J., and Kletzhändler, M.: (Abstr.) *J. A. M. A.* 116: 786, 1941.
10. Wyrens, R. G., and Randall, L. M.: *Am. J. Surg.* 56: 395, 1942.
11. Schneider, Paul: *Am. J. Roentgenol.* 48: 527, 1942.
12. Geist, S. H., and Goldberger, M. A.: *Surg., Gynec. & Obst.* 41: 646, 1925.

THERAPEUTIC ASPECTS OF UTEROTUBAL INSUFFLATION IN STERILITY*

I. C. RUBIN M.D., F.A.C.S., NEW YORK, N. Y.

DURING the past three decades considerable progress has been made in the diagnosis and therapy of sterility. The very concept of sterility has been subjected to newer interpretations and qualifications. Thus Reynolds has suggested the term infertility to be applied to that group of women whose reproductive ability is temporarily lowered, the deficiency being amenable to treatment. Until recently, tubal obstruction was regarded as an absolute and irremediable cause of sterility. In 1919, Giles¹ considered "tubal disease one of the quite definite and incurable causes of secondary sterility as it is of primary sterility." This statement may now be qualified, due to progress made with use of uterotubal insufflation, to the use of x-rays combined with opaque media and other physical measures, exclusive of plastic surgery. By these nonsurgical measures, it has been possible to re-establish tubal patency in some cases when surgery is otherwise contraindicated or refused by the patient.

In the present paper, I have endeavored to estimate the therapeutic value of uterotubal insufflation in sterility. The study is based on the pregnancies that have taken place in my own series as well as the series reported by others. In my cases, no specific follow-up was made. The patients volunteered the information directly in some instances or they took occasion to transmit the report through the kindness of other patients whom they referred for diagnosis and treatment. For these reasons the percentages adduced lack definitive statistical value which only a complete and systematic follow-up would have yielded.

Although I have considered uterotubal insufflation primarily as a diagnostic procedure, its therapeutic possibilities have been stressed by others. First amongst these were Peterson and Cron^{2, 3} and Rongy.⁴ Since then there have been an increasing number of reports.

Modus Operandi.—The question of how insufflation aids the sterile woman, has from its inception engaged the interest of many. Peterson and Cron^{2, 3} sought early in their experience with the therapeutic application of the insufflation test to explain the higher percentage of pregnancies in women who were secondarily sterile. They suggested that "something more than the mere passage of the gas and the mechanical opening of the tubes by insufflation must be considered." An exact explanation for the way in which insufflation aids the sterile woman cannot always be given. For the majority of successful cases, however, the therapeutic action appears to be the following:

1. *Establishing Patency of the Genital Tract.*—Insufflation establishes patency of the genital tract from the external os of the cervix to the abdominal

*Read by invitation before the Boston Obstetrical Society, March 20, 1945.

opening of the Fallopian tubes. Any cervical canal that is patulous to the uterine cannula employed in the procedure is ample for the entrance of spermatozoa. If the external os appears punctate or pin-point but admits the cannula, this is proof that it is wide enough to admit semen into the external opening of the cervical canal. The cannula at the same time stretches it somewhat, rendering the canal more patent for a varying period of time. Should intercourse take place shortly after this procedure, the spermatozoa have a better opportunity to enter the uterine cavity.

In this respect the procedure may be compared to the former practice of introducing a sound, which was frequently followed by pregnancy and believed by older gynecologists to be the result of the uterine sounding. In my series there was one case with a definite stricture of the cervix where the introduction of a uterine sound was shortly followed by pregnancy.

The patient was 27 years old and infertile for five years following the birth of a first child. She was examined just before an expected menstrual period which, however, was skipped, the Aschheim-Zondek test being positive two weeks later. Whether or not the sound had therapeutic value or was coincidental to an already existing pregnancy is not ascertainable. Strongly suggestive of the latter possibility is the fact that the procedure was carried out shortly before the next menstrual period. The case illustrates the difficulty commonly met with in endeavoring to give deserved credit to whatever measures may have been employed in sterility before conception takes place and the importance of analyzing all the circumstances connected with the case. The introduction of the cannula by itself has in all probability minor therapeutic value.*

2. Removal of the Cervical Mucus Plug.—In some cases a mucus plug, not visible at the external os but occupying the deeper portion of the cervical canal, is expelled after the cannula has been removed. I have the impression that the dislodgment of the mucus plug may be the important factor in a number of the earlier cases. In the past few years I have employed suction preliminary to the introduction of the cannula, thus clearing the cervical canal of the deeply lodged mucus plug.

Menchikoff⁵ believes that the distention of the uterine cavity and the stretching of the internal os are often beneficial. Devraigne and Seguy⁶ state that insufflation favors the ascent of spermatozoa by dilating the tubes in a way similar to dilation of the cervix.

3. Effect on the Tubes.—Insufflation probably exerts its most valuable therapeutic action on the tubes. Its manifold action consists in separating mild agglutinations of the folds of the tubal mucosa, straightening out tortuous tubes, especially of the infantile type (this must be only temporary), dislodging a mucus inspissation from a narrow to a wider portion of the tube, and actually separating adhesions at the fimbriated end in cases requiring pressures of 150 to 200 mm. Hg or more. In this manner a way is opened for the descending ovum to meet the ascending spermatozoa. Coghlan,⁷ Hamant,⁸ Floresco and Naum,⁹ Geppert,¹⁰ Rongy and Rosenfeld,¹¹ Sellheim,^{12,13} and others have offered this explanation, which was ventured in 1925.¹⁴

*In discussing this paper at Boston, Dr. John Rock stated that he had endeavored to check the value of introducing a uterine sound into the uterine cavity in 75 cases but encountered no pregnancy in his follow-up.

Hirst and Mazer¹⁵ believe that the therapeutic action is often exerted on tubes which are nonpatent as a result of a blockade left in the wake of a catarrhal salpingitis which has remained unrecognized. With subsidence of this acute condition which is marked by increased secretion and thickening of the mucosa, accompanied by some destruction of the cilia, there still remains sufficient inspissated mucus in the tubal lumen to occlude it. They compare this condition to that found in the Eustachian tubes. "A retracted drum head means to an otologist insufficient ventilation of the middle ear due to occlusion of the Eustachian tube, structurally not unlike the Fallopian tube. To relieve this condition, the otologist resorts to inflation of the nasopharynx under pressure with the Pollitzer bag. He is frequently forced to make several attempts before he succeeds in opening the Eustachian tubes."

Peterson and Cron^{2, 3} insufflated agglutinated tubes during laparotomy. When a pressure of 200 mm. Hg or more was reached, the gas was seen to be expelled into the peritoneal cavity either by a separation of the adhesions or by rupture of the infundibulum at the weakest avascular point of the tube, about 1 cm. from the closed fimbriated end. The opening, at first small, was enlarged by the continual escape of gas. They suggest the advisability of using high pressures, as high as 300 mm. Hg at operation, having found that in every instance rupture occurred at the infundibulum with no appreciable hemorrhage at any time. Either the adhesions separated or the tube ruptured at an avascular portion.

That pregnancy results from mechanical separation of adhesions through tubal insufflation has been observed at cesarean sections in the two following cases:

D. M., 29 years old, had been married for one year. She had a spontaneous miscarriage about three months after marriage and had not been able to conceive since then. On Aug. 7, 1933, tubal patency was demonstrated at a pressure of 208 mm. Hg, dropping in a parabolic curve to 68 mm. Hg. About three months later the patient conceived and was delivered by cesarean section on Aug. 29, 1934. Inspection of the adnexal regions showed that the right tube and ovary were bound down to the fimbria by adhesions which connected the tube and ovary with the posterior lateral aspect of the uterus. The adhesions connecting the left tube to the ovary were found to be broken and hung like long strands. These had evidently been broken through by the insufflation. Insufflation on Jan. 14, 1935, indicated tubal patency at a pressure of 99 mm. Hg. Auscultation was very loud on the left side and faint on the right side. About nine months later the patient conceived again, and was delivered by cesarean section, June 29, 1936. Insufflation on Feb. 16, 1937, showed retained tubal patency. (Figs. 1A and 1B.)

M. P. was a nullipara, married six years, with involuntary sterility for the past two and one-half years. Two and one-half years ago she had had an operation which was thought by the patient to have been a ventrosuspension and removal of her left tube and ovary. Uterotubal insufflation done elsewhere eight months ago showed tubal patency. The patient had always had severe dysmenorrhea, and hypomenorrhea had set in of late. During insufflation on Jan. 15, 1932, the pressure rose to 95 mm. Hg, then with further obturation rose to 172 mm. Hg, dropping to 128 mm. Hg. Fluoroscopy demonstrated a right subphrenic pneumoperitoneum. She conceived that same month, and was delivered by cesarean section, Oct. 7, 1932. At operation, the uterus was found fixed to the left by peritoneal and omental adhesions. The right ovary was found slightly enlarged, the right tube was bound down at the fimbria to the ovary and mesosalpinx by loose bands of adhesions. The left tube and ovary were absent.

Although artificial rupture can be free from harmful results, forcible opening of pathologic tubes requiring the use of high pressure should never be done deliberately except by the expert. With the abdomen open, higher pressures may be ventured. The possibility of producing gas embolism is obviated

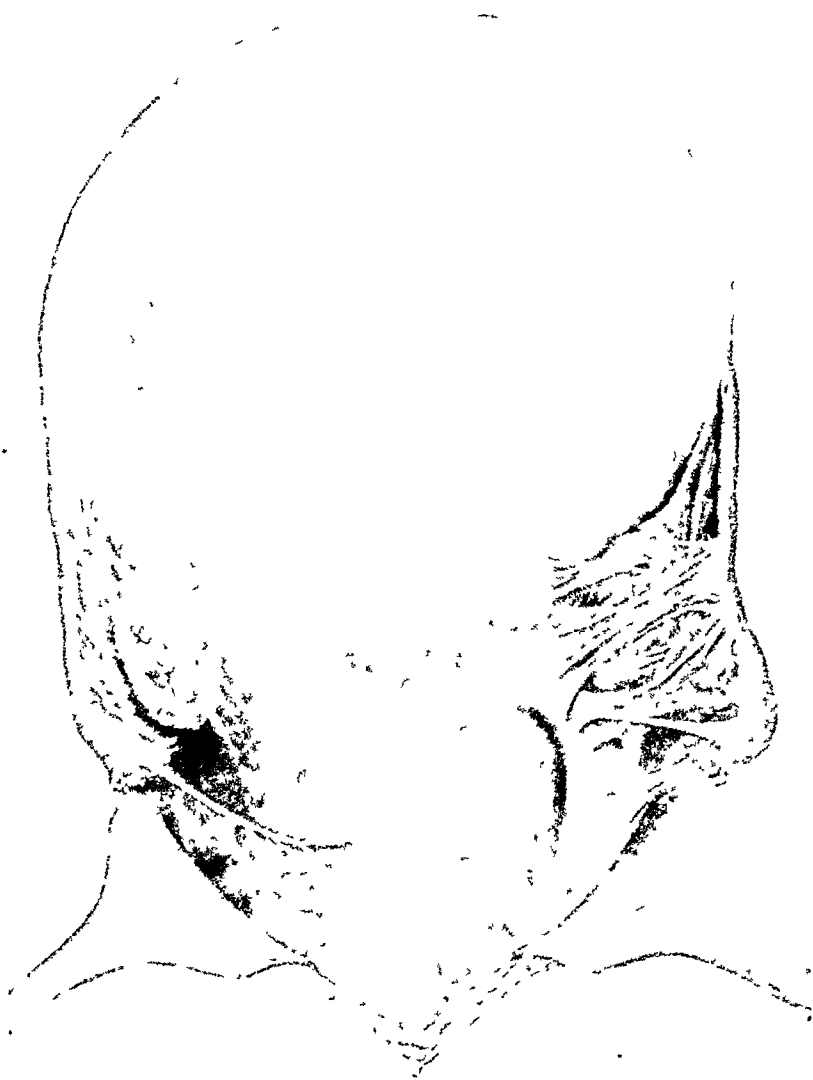


Fig. 1A.—Both tubes are adherent to the ovaries. The fimbriated ends show through the adhesions, which are evidently fragmented, more especially on the left side. It is presumed that the ovum was carried through the left fimbria.

by careful avoidance of intrauterine trauma. This applies particularly when other gases, including air, are used instead of carbon dioxide, which has proved to be the gas of choice. Pressures above 200 mm. Hg have been employed by some individuals, using either gas or fluid. In the absence of palpable tenderness and of pelvic masses, careful uterotubal insufflation may be carried out, employing pressures beyond the recommended maximum with the prospect of opening tubes that resist lower pressures, the increment of risk to the patient being minimal.

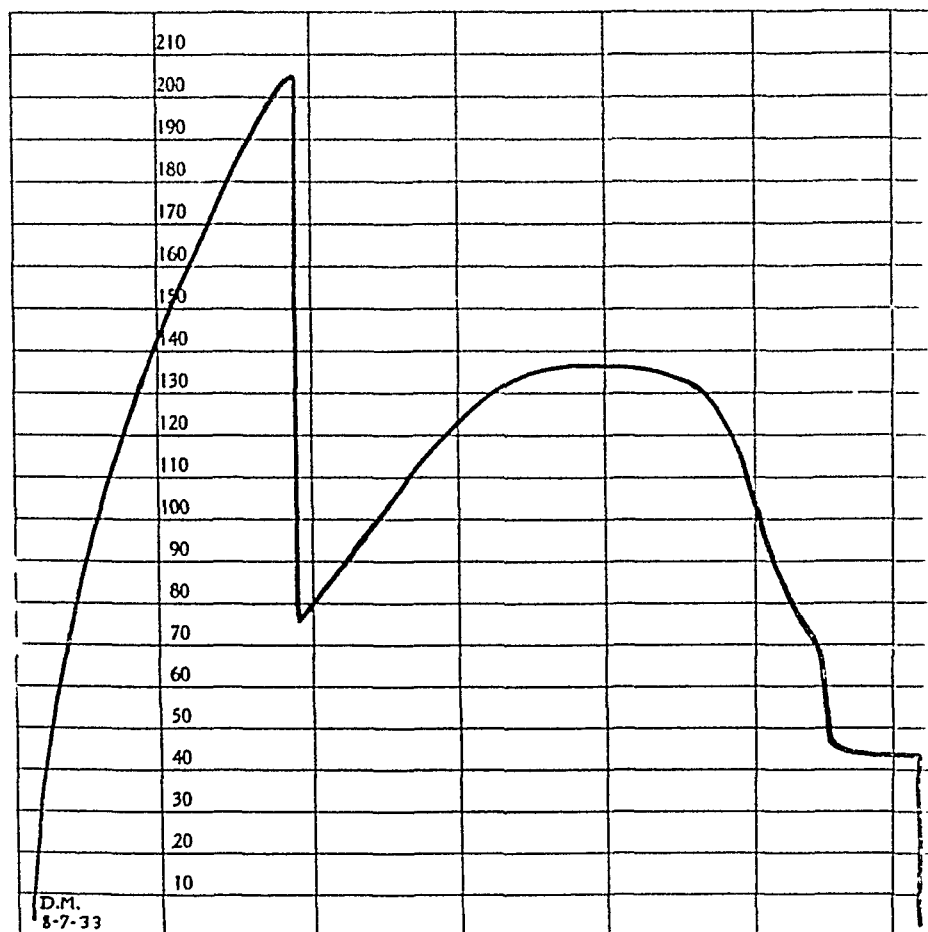


Fig. 1B.—Reconstructed tubograph, Aug. 7, 1933, showing an initial rise of pressure to 205 mm. Hg with a sharp drop to 76 mm. Hg, following which the pressure rose to 136 mm. Hg in a paraboloid fashion, dropping to 48 mm. Hg when the gas valve was shut. The fimbrial adhesions apparently of the left tube were broken through at 205 mm. Hg. as seen at the laparotomy for cesarean section.

Clinical experience with reopening ligated tubes by uterotubal insufflation illustrates the therapeutic value of this procedure with the convincing force of experimental corroboration. Figs. 2A and 2B show the tubographs in the first case in which ligated tubes were successfully reopened in this way.

The patient, D. S., aged 37 years, had had a cesarean delivery, at which time the Fallopian tubes were ligated. Contemplating remarriage after divorcing her husband, she wanted to know whether she could become pregnant again. This was made possible by uterotubal insufflation which opened the tubes at a pressure of 167 mm. Hg. She became pregnant shortly after her second marriage.

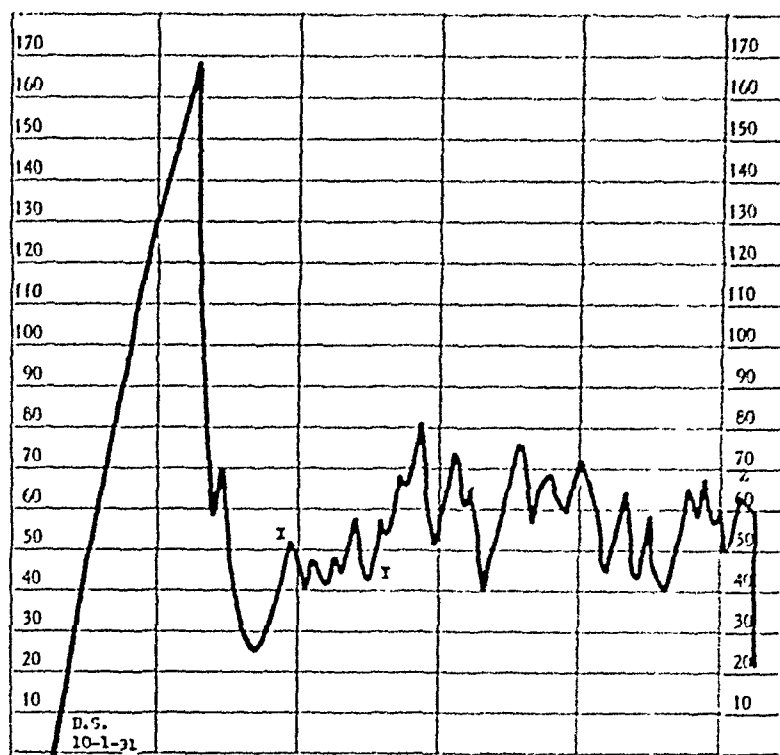


Fig. 2A.—Tubograph, Oct. 1, 1931, in case of patient D. S., showing the therapeutic effect of opening ligated tubes. Pressure rose to 160 mm. Hg, following which there was a sharp drop to 60 mm. Hg and to 25 mm. Hg, indicating the breaking through of the ligated tubes. Restoration of tubal patency and function is indicated in the graph from *x* to *z*. Pain was complained of on the left side at *x* and on the right side at *y*.

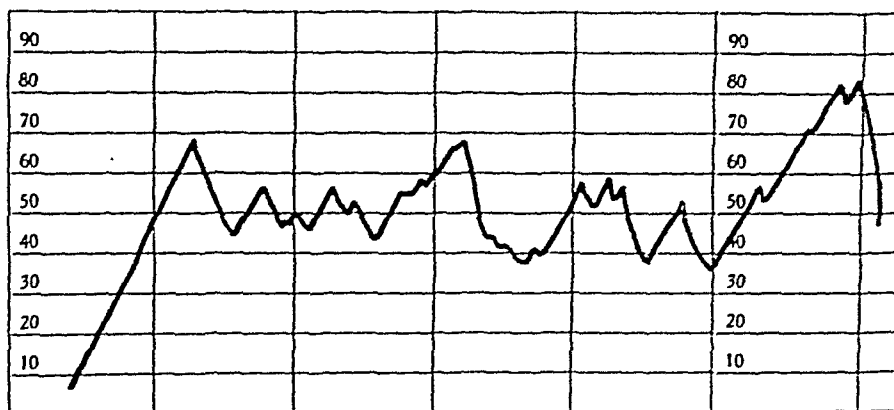


Fig. 2B.—Tubograph in the same case, Oct. 11, 1937, indicating normal tubal patency. Pregnancy had intervened between these two insufflations.

4. *Possible Psychic Effect.*—A factor not to be ignored is the psychic effect produced by uterotubal insufflation. Although the exact mechanism is not clear, there are women who respond to insufflation through the psyche acting on the autonomic nervous system. Whether or not this results in a relaxation of otherwise spastic tubes must await further inquiry.

We have met, in certain tubes, with spasms sufficient to close the uterine ostia in a manner similar to the closure of the internal os of the cervix. Overcoming such spasm may obviously exert a therapeutic effect. Pouliot¹⁶ reports two instances of uterotubal spasm where pregnancy followed insufflation. I have had a similar experience in twenty cases.

Another possibility is the occasional hastening of follicle rupture, particularly in women whose emotional psychic reaction to the insufflation inaugurates an orgasm during the next marital relation when it would otherwise be absent. The matter of coincidence must be considered in this respect. No actual proof is at hand of an ovulation thus provoked. Whether the psychic reaction produces on some occasions follicle rupture similar to that which invariably follows coitus in the rabbit is purely a matter of speculation and falls into that category of suggestive therapeutics of which the Fliess treatment affords a notable example.

Lane-Roberts, Sharman, Walker, and Wiener,¹⁷ bearing in mind the possible stimulating effect of insufflation upon the endocrine system, prefer to withhold its use to the month preceding the cycle during which investigation of the hormonal functions in any given case is carried out. These authors state that "although there is no definite evidence that the therapeutic results of this procedure may be accounted for in part by its stimulating effect on endocrine function, this possibility cannot be wholly excluded."

5. *The Therapeutic Effect of Repeated Tests.*—When the tubes were found to be obstructed, the test was repeated not only for diagnostic corroboration but also for its therapeutic effect. For this purpose as many as 18 tests were performed on one of my personal cases.

A therapeutic tubal effect may be deduced under the following circumstances: (1) when the initial rise of pressure is lower at a second or third insufflation, and (2) when the level at which the pressure is maintained is likewise lower. Not infrequently one meets with a return of tubal function which is demonstrable on the kymograph.

A most striking therapeutic result was seen in women whose tubes were insufflated several times, nonpatency being encountered at a first or second test and patency at a subsequent test, and who became gravid shortly after the last insufflation. Under these circumstances it seemed justified to credit insufflation with the successful result. Twenty patients in my series, in whom a single test showed a pressure of 200 mm. Hg, nevertheless became gravid. In these cases either a small amount of gas was forced through strictured tubes, the amount being insufficient to produce a subphrenic pneumoperitoneum and shoulder pains, or uterotubal spasm actually resisted the passage of CO₂ at a pressure of 200 mm. Hg.

Repeated ectopic pregnancy may result despite pressure of 200 mm. Hg or more being encountered during insufflation.

This was found in the case of R. A., a 33-year-old woman, who had a right salpingectomy for ruptured tubal pregnancy, two years after marriage. Repeated uterotubal insufflations with pressures of 200 mm. Hg or more produced no shoulder pains and no subphrenic pneumoperitoneum, thus indicating an obstructed residual tube. One year after the last insufflation, she was operated on for ruptured ectopic gestation in the left tube.

To what extent repeated insufflation may improve the tubal status from high-grade strictures to varying degrees of patency may be seen in Table I.

TABLE I. THERAPEUTIC EFFECT OF REPEATED TESTS

	NUMBER OF TUBAL CASES	NUMBER OF IMPROVED	PER- CENTAGE
Tubal obstruction; maximum pressure 200 mm. Hg	939	185	19.70
Adherent and strictured tubes; maximum pressure 200 mm. Hg or less	917	238	25.95
Uterotubal spasm; maximum pressure up to 190 mm. Hg	134	15	11.19

Altogether, there were 438 patients whose Fallopian tubes showed improvement in patency on a second or third insufflation. Sixty-six of these women became pregnant (15.07 per cent). It is noteworthy that 79 of the 238 patients with adherent and strictured tubes showed a normal curve following several insufflations.

In Weitzner's¹⁸ series of 250 sterility cases, tubal obstruction was reduced from 38 to 27 per cent by a second insufflation. Abbott¹⁹ reported a series of 51 cases of occluded tubes. Four of these patients became pregnant following the opening of the tubes by repeated insufflations; no other measures had been employed. Twenty-eight other patients became pregnant following repeated insufflations combined with other forms of therapy.

In Douay's²⁰ series of 100 women with "closed" tubes, patency resulted after repeated insufflations in 18 cases; 5 of these became pregnant (28 per cent). Graff^{21, 22} found 44 per cent of his patients to have nonpatent or partially obstructed tubes. Twelve per cent of his cases became patent after repeated tests, and of these 14 of 43 cases became pregnant (32.6 per cent). Davis²³ succeeded in opening the tubes under pressure in 8 of 13 cases with "closed tubes" and 3 of these patients became gravid.

Pouliot¹⁶ observed 14.4 per cent pregnancies, i.e., 24 of 167 women with permeable tubes, whereas 14 of 43 women whose tubes were made permeable became gravid, i.e., 32.6 per cent. In Meaker's experience, the gas passed through the tubes after much difficulty in the first trial in two patients and in another patient only at the fourth attempt. Two of these patients became gravid at once and the other after two months.

Mintz²⁴ established patency in 25 out of 44 cases by repeated insufflation and diathermy. Eleven of these patients became pregnant.

The results just mentioned in a combined series aggregating over one thousand cases call attention to the fact that we must revise our notion of what constitutes tubal closure and it becomes necessary to define the term "closed tubes." A hydrosalpinx is the classic representation of a closed tube which is watertight and therefore airtight. The clubbed fimbriated end is another example of a closed tube. There are, however, many degrees of nonpatency, varying from the mild agglutination of a few mucosal folds to light adhesions about the fimbria, including phimosis, all of which may be said to render the tubes unfit for their physiologic function, namely, to convey the ovum toward the spermatozoa.

There is no doubt that occasionally these impediments disappear spontaneously, permitting conception to take place, and pregnancy develops normally. Not infrequently, however, the impregnated ovum is trapped in the tube or more rarely even in the ovary.

As we have seen, thanks to Peterson's experimental observations during laparotomy, closed tubes in the truest sense may be opened by employing sufficiently high pressures. In many of the other relatively closed or nonpatent tubes it is possible to widen the strictured lumen by more moderate pressures. From the therapeutic point of view this is of the greatest importance, as experience has repeatedly demonstrated.

We are, therefore, in a position to state that, within certain clinical and pathologic limits, practically all Fallopian tubes fall into three groups: (1) normally patent tubes; (2) nonpatent tubes; (3) intermediary. With adequate pressures, Group 2 may be advanced to Groups 3 and 1; Group 3 may be more readily restored to Group 1, i.e., normality.

Group 1 refers to tubes where patency is demonstrable upon the first trial with insufflation, the pressure noted being at 100 mm. Hg or less, and good contraction waves or oscillations are recorded on the kymograph. Group 2 includes tubes that do not yield to pressures of 200 mm. Hg in two or three tests. Group 3 includes tubes that show relatively high pressures but some slight patency in the first or second test.

The extent to which some degree of patency can be produced by tubal insufflation alone or by any additional measures, such as diathermy treatment or the more potent hormonal extracts, will determine the conceptional possibilities in women whose sterility is traceable chiefly to tubal pathology. It is with this object in mind that the following statistical analysis has been made in 590 personal cases of pregnancy preceded by uterotubal insufflation.

Five hundred and ninety cases of pregnancy occurred after insufflation in 3,200 cases. The well-known tendency of ascribing to any new method of treatment an occasional successful result in the sense of *post hoc ergo propter hoc* applies equally to insufflation. There is no doubt that many patients have become pregnant after a shorter or longer interval following an insufflation which has demonstrated normal tubal patency. Obviously the diagnostic test may have had no etiologic connection, the ever-present element of chance and coincidence playing its part. In order to offset this it has seemed to me necessary to venture certain reasonable criteria which would serve more adequately to estimate the therapeutic value of insufflation.

A therapeutic result may be deduced when the following conditions are met:

1. The age of the woman is 30 years or over.
2. The length of marriage is three years or longer.
3. No other therapeutic measure was employed.
4. The insufflation was done within the first two weeks of a last regular period (in preovulation phase).
5. No contraceptive precautions were taken for at least one year prior to the test.
6. Pregnancy follows within a month or at most two months after tubal insufflation.

7. Pregnancy follows after repeated insufflation; a relatively lower pressure sufficing to demonstrate patency on a second, third, or fourth test.

8. Pregnancy follows the third month after one insufflation during which a high initial pressure was necessary and the tubes were found to be strictured or adherent. Obviously the element of chance may be regarded as minimal.

Primary Versus Secondary Sterility.—In my personal series there were 2,014 patients in the group of primary sterility. Of these, 358 (17.77 per cent) became gravid. There were 1,186 patients with secondary sterility of whom 232 (19.56 per cent) became pregnant. Altogether, 590 women were reported pregnant out of 3,200 cases, making the total percentage 18.44. This percentage may not be taken as final because only 590 patients voluntarily reported their pregnancy either directly or through a patient referred by them for treatment.* It is probable that others may not have thought it of interest to communicate the fact of their pregnancy at once or later, while a not inconsiderable number remember to do so after the birth of a second or possibly third child. For obvious reasons a routine follow-up questionnaire was not submitted to patients. In a number of instances the report came from the family physician. Inquiry of colleagues employing tubal insufflation had been made in 1928, the response to which has been tabulated. An additional series was reported by a larger number who replied to a recent questionnaire.

To what extent insufflation was helpful in the 232 cases of secondary sterility may be seen from the way in which the pregnancies had terminated prior to treatment (Table II).

TABLE II. PREVIOUS PREGNANCIES OF 232 SECONDARY STERILITY CASES

	NUMBER	PERCENTAGE
Term babies	74	31.8
Tubal pregnancies	19	8.2
Stillbirths	11	4.7
Spontaneous abortions	70	30.2
Induced abortions	35	15.1
Abortions—type not stated	23	10.0
Total	232	100.0

The slightly greater success following insufflation in the secondary sterility cases may be mere coincidence (19.56 per cent as compared with 17.77 of primary sterilities). On the other hand, since these patients had already demonstrated their ability to conceive, it may indicate the more frequent occurrence of tubal obstructions as a result of puerperal or abortal infection, which the mechanical act of insufflation may be credited with overcoming.

Age of Patients.—The age of patients who became gravid is important from the standpoint of the therapeutic effect, as it must be in considering the value of any other therapeutic measure that might be employed in sterility (Table III).

One hundred and forty-six patients were between the ages of 20 and 25 years, and 250 between the ages of 25 and 30 years. One hundred and eighty-

*Since the collection of the above data 82 additional cases have been recorded. The statistics were compiled by Dr. Morris Feresten.

TABLE III. AGE OF PATIENTS

AGE (YEARS)	NUMBER	PERCENTAGE
15-20	10	1.69
20-25	146	24.75
25-30	250	42.37
30-35	144	24.41
35-40	34	5.76
40-45	6	1.02
Total	590	100.00

four, or 31.19 per cent, were 30 years of age or over when they sought relief; 34 of these were between the ages of 35 and 40 years, and six were over 40 years old.

Length of Marriage.—In any consideration of the treatment of sterility, it is important to take into account the question as to how long after marriage we shall wait before encouraging a married couple to seek relief from sterility. A period of three to four years has been previously regarded as ample time to judge whether a marriage is sterile. This figure is obviously arbitrary, for some women have become pregnant long after this interval. On the other hand, serious difficulties in the way of conception may exist soon after marriage and not infrequently even before marriage. Giving Nature a prolonged trial in such cases merely delays corrective treatment which may require a relatively long period of time. Other things being equal, the younger the patient is, at the time the cause of her sterility is discovered and removed, the greater are her chances to benefit by treatment.

TABLE IV. DURATION OF MARRIAGE

DURATION (YEARS)	NUMBER	PERCENTAGE
1- 3	225	38.14
3- 5	154	26.10
5-10	170	28.81
10-15	38	6.44
15-20	3	0.51
Total	590	100.00

In this series, 225 women, or 38.14 per cent, were married from one to three years when they sought relief from childlessness (Table IV). The reasons why these patients applied for relief early were varied. Thus, one young woman was ardently desirous of an offspring for reasons concerning the settlement of an estate. Another had witnessed the difficulty encountered by two older sisters who became pregnant from three to five years after marriage. One patient was over 40 years of age and felt that she had only a short childbearing period left to her. She sought advice within a few months after marriage. Several had been married to a first husband for a number of years without conceiving. Consummating a second marriage, it was not surprising that they endeavored, after waiting only a short time, to discover the cause of their infertility. A few had had an only child and dreaded the thought of bringing up a solitary child.

Thus, there are various circumstances, social, economic, domestic and some of private personal nature, that impelled this small group of patients to seek a

solution. The majority (61.86 per cent), however, had been married over three years, 41 having been married ten years or longer.

Average Time of Conception Expectancy.—In any analysis of the end results of a therapeutic procedure in sterility it is well to take into account the natural expectancy of conception among couples after variable lengths of married life.

Coghlan⁷ found that only 295 women, approximately 3 in ten thousand, out of 1,001,383 married women in Australia had a first child after being married ten years or longer. He estimated the incidence of a first pregnancy in women married fifteen years or over at 0.005 per cent (one in twenty thousand).

G. Kaboth and J. Kleefisch³² analyzed the marital history of 5,331 couples in order to estimate the natural incidence of spontaneous conception. Their figures serve the useful purpose of comparison with the results obtained by therapeutic measures applied in the treatment of sterility.

In my series of cases of secondary sterility, the length of time elapsing from the last pregnancy, whether it terminated in abortion or full-term pregnancy, was reckoned as equivalent to a period corresponding to the duration of primary sterility. If contraceptive measures were used, the period of involuntary sterility was measured by the interval elapsing from the time they were discontinued. (Table V.)

TABLE V. DURATION OF STERILITY (PRIMARY AND SECONDARY)

DURATION (YEARS)	NUMBER	PERCENTAGE
1-3	285	48.31
3-5	162	27.46
5-10	127	21.53
10-15	14	2.37
15-20	2	0.33
Total	590	100.00

Comparison With the Natural Expectancy of Conception.—After the third year, three times as many patients became pregnant as might be expected according to natural incidence. After seven years, the patients' chances are increased many times by insufflation; and after ten years, according to Coghlan's estimates, insufflation appears to improve proportionately the chances of pregnancy. The two patients who became pregnant after having been sterile for fifteen years show an incidence of one in 1,600, as against one in 20,000 according to Coghlan's figures. When it is considered that 34 of my patients were between the ages of 35 and 40 years, and six were over forty years, the 40 pregnancies in this group may be accepted as due to therapeutic efforts rather than chance.

Use of Contraceptive Precautions.—Of the 590 patients who became gravid following insufflation, 190, or 32.20 per cent, had used precautions at some time of their marital life. In 97 of these, an interval of at least two years had elapsed since they stopped contraceptive precautions. Fifty-four patients had used no precautions for three to seven years before seeking relief. The remaining 39 patients had ceased the use of precautions for one year before insufflation.

Many women employ precautions only to find out to their surprise, after discontinuing the practice, that they cannot become pregnant. How the use of

preventive measures affects the reproductive organs of the female, rendering her less susceptible to conception is still a matter of conjecture. It may be presumed that the use of chemicals such as Lysol douches, bichloride of mercury and even less corrosive solutions possibly alter the vaginal and cervical mucosa and their normal secretions. The bacterial flora which are usually present in the vagina, and which favor the spermatozoa, may possibly be disorganized by the frequently repeated use of antiseptic douches, pessaries, and other devices. On the other hand, the practice of withdrawal is not unlikely attended by sequelae as yet not understood, which may exert a deleterious influence on the mechanism of conception. It must, however, be noted that a not inconsiderable number of women practice contraception whose Fallopian tubes are blocked and hence could not conceive if they took no precautions, while, in some cases at least, the male may be sterile without knowing it.

The Male Factors.—In analyzing the factors involved in sterility we cannot omit the male factor. It is important to note the degree of potency and character of the sperm output. Many women, already handicapped by their own lowered fertility, were still further burdened by a mate with reduced fertility. In some cases, the male alone may have been responsible for the sterility. None of the patients in this group were insufflated until there was satisfactory evidence of intromission and the production and quality of the sperm were determined. The Huhner test was employed and whenever necessary the unmixed specimen of semen was examined. If the wife came from some distant town unaccompanied by her husband, the data concerning the male partner were usually furnished by the family physician. Such information was obtained in 66 cases.

In 320 cases the husband was considered potent and satisfactory. In 193 cases there was a mild oligospermia; 64 of these, as demonstrated by later examinations, showed improvement after treatment by diet, advice about coitus, and the like.

Eleven husbands had a marked oligospermia. In 10 of these cases the spermatozoa were so few that they could not be found in the vaginal or cervical secretions when a single Huhner test was made; in another case two examinations failed to reveal the presence of spermatozoa. In these 11 cases, a condom examination, were it feasible, might have shown the presence of spermatozoa. Unless the patient frankly avows the resort to substitution, it is naturally impossible by the Huhner test alone to determine the fertility of the legitimate mate. This criticism applies equally to the examination of the condom specimen.

In a number of cases there was lowered fertility of both the male and female partner. Improvement in tubal patency following insufflation of tubes which were partially occluded, and improvement in the seminal output on the part of the husband raised the combined fertility to a point where conception took place. Occasionally, inseminating the wife artificially at such a favorable time results in pregnancy after one trial.

This was encountered in L. T., a 24-year-old woman who had been married for four years without being able to conceive. Uterotubal insufflation done elsewhere showed incom-

plete tubal obstruction, shoulder pains appearing after one-half hour. On Nov. 30, 1926, a kymographic insufflation showed obstruction to a pressure of 150 mm. Hg, when there was a gradual drop to 100 mm. Hg, after which shallow oscillations were recorded. The husband had oligospermia, for which he was later treated. On March 21, 1933, the tubes were found to be obstructed at a pressure of 190 mm. Hg when the gas passed through, the pressure dropping to 115 mm. Hg, following which shallow oscillations were again recorded. On Jan. 30, 1934, the obstruction was noted at a level of 205 mm. Hg at the first insufflation. The gas began to flow through at the second trial at 200 mm. Hg. At this time there was present uterotubal spasm in addition to stenosis which was characterized by pain and discomfort localized at the midline above the symphysis pubis. The patient was extremely desirous of becoming pregnant and, having brought in a sterile jar an ejaculate of semen which proved to be normal in all respects, the semen was poured into the vagina where it was left for an hour while the patient lay in the Trendelenburg posture. She conceived promptly and had a normal child Oct. 10, 1934.

Subsequently, Feb. 19, 1937, uterotubal insufflation showed normal patency and good oscillations indicating good rhythmic tubal contractions (Fig. 3).

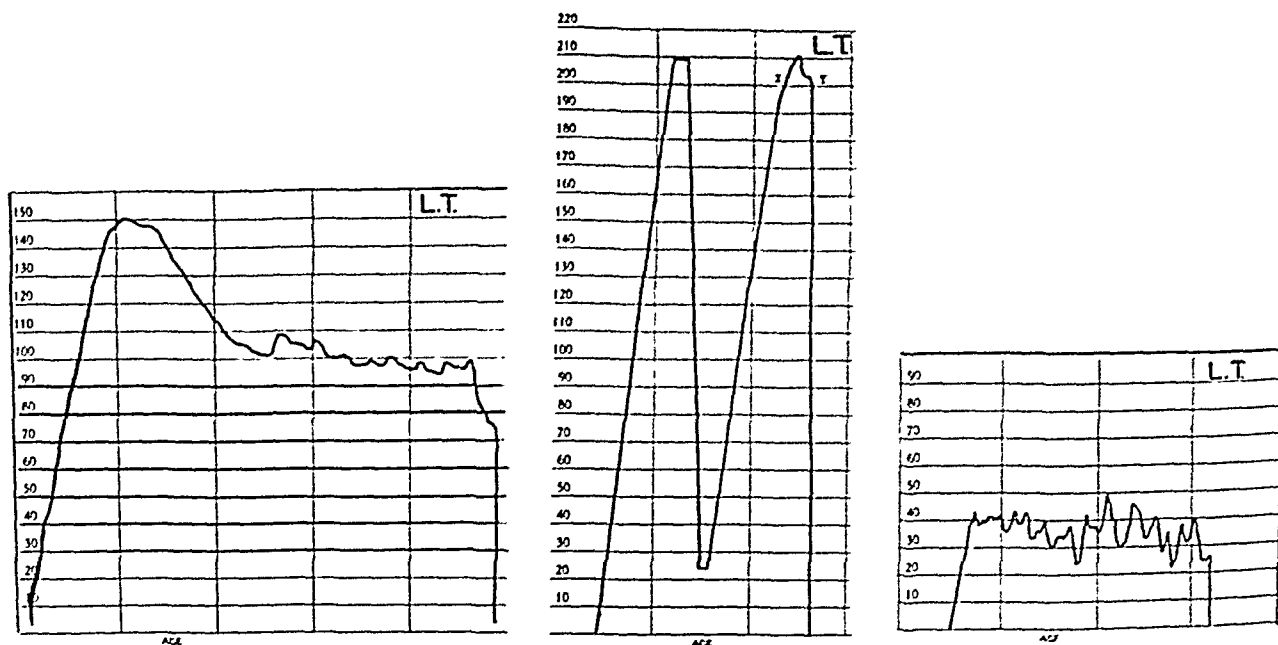


Fig. 3.—A, Tubograph, Nov. 30, 1926, showing tubal narrowing. B, Tubograph, Jan. 30, 1934. Note *xy*, the rounding of the curve, indicating a slight degree of patency in addition to spasm. C, Tubograph, Feb. 19, 1937, showing practically normal tubal patency and function as a result of intervening pregnancy with its estrogenic influence on the tubes.

The Tubal Factor.—Insufflation was the only treatment employed in 386 of the 590 patients who became pregnant (65.42 per cent). The therapeutic measures employed in the remaining 204 cases are too varied for evaluation.*

Table VI shows that 46.44 per cent of the pregnancies occurred in women whose Fallopian tubes exhibited various degrees of impaired patency.

The incidence of pregnancy in the general sterility group according to the status of the tubes is shown in Table VII.

*Important as they are in considering general therapeutic treatment in sterility which includes artificial insemination, details concerning them are not entered into here because it is our special task to evaluate the tubal factor. In this connection it may be well to emphasize the desirability of determining the fact of tubal patency before subjecting the patient to an artificial insemination.

TABLE VI. TUBAL STATUS IN 590 PATIENTS WHO BECAME PREGNANT

	NUMBER	PERCENTAGE
Normal patency	316	53.56
Adherent tubes	135	22.88
Strictured tubes	118	20.00
Spasm and normal patency	21	3.56
Total	590	100.00

TABLE VII

	NUMBER OF CASES	NUMBER OF PREGNANT CASES	PERCENTAGE
Normal patency	1,210	316	26.12
Adherent tubes	538	135	25.09
Strictured tubes	379	118	31.13
Spasm and normal patency	134	21	15.74
Total	2,261	590	98.08

The therapeutic effect of insufflation is particularly noteworthy in the 118 cases of strictured tubes which resulted in pregnancy in 31 per cent as against 26 per cent of the cases with normal tubal patency.

There were five additional cases with incomplete tests who became pregnant. The cervical canal was strictured in one case; the uterine cavity was probably not entered but the patient promptly became gravid.

In one case a pressure of 200 mm. Hg was reached. The patient weighed 160 pounds, and, as about 60 c.c. of gas was introduced, only the smallest part of it entered the peritoneal cavity through the strictured or spastic tubes. There was insufficient gas to produce a visible pneumoperitoneum or shoulder pains, and the patient was advised to have the test repeated the following month. This was not necessary as she became pregnant the same month. In another case the gas passed through freely at a low pressure but not enough gas was introduced to produce the typical subphrenic pneumoperitoneum and shoulder pains. She became pregnant. In one case the first and only insufflation showed a pressure rise to 160 mm. Hg and all the indications of patency were not present. In the fifth case data were lacking for a diagnosis of the tubal status.

Occasionally the fluoroscope fails to reveal a subphrenic pneumoperitoneum although the pressure shows a definite tendency to drop from a high level during the insufflation, indicating some degree of tubal patency which is further substantiated by the appearance of shoulder pains. In such cases I have felt that the diagnosis of patency should be held in abeyance till all the signs and symptoms of a subphrenic pneumoperitoneum are manifest. Should it be important to make the diagnosis at once, it is only necessary to prolong the flow of gas for another minute or two, when all the pathognomonic signs and symptoms may be elicited. This small group with incomplete tests has an interesting relationship to the therapeutic aspects of insufflation. As only 5 of the 142 women (3.5 per cent) who were classified amongst the incomplete tests became pregnant, compared to an average of 18.43 per cent who had a complete test, it may be construed as a check on the therapeutic efficacy of insufflation.

Initial Rise of Pressure.—The initial rise of pressure at which the gas passed the uterotubal junction in these 590 cases gives us another angle from which to judge the therapeutic effect of uterotubal insufflation.

TABLE VIII. INITIAL RISE OF PRESSURE

	NORMAL PATENCY	ADHESION	STRICTURE	SPASM
Under 50 mm. Hg	28			
50 to 100 mm. Hg.	241	74		
100 to 150 mm. Hg	47	61	35	10
150 to 200 mm. Hg			54	8
200 mm. Hg plus			29	3

Of the 590 patients, 247 or 41.86 per cent, had initial pressures above 100 mm. Hg, which may be taken as evidence of impaired patency. The therapeutic effect of insufflation is particularly noteworthy in the 94 cases in which pressures of 150 mm. Hg and over were required for the gas to pass through the tubes.* Repeated insufflations improved the status in many of these cases before pregnancy took place. Thus, among the patients who became pregnant following insufflation, the test was repeated once in 104 patients, twice in 37 patients, three times in 16 patients, four times in 10 patients, five times in 3 patients, six times in 5 patients, seven times in each of the 4 remaining patients. These 179 patients had therefore received 526 tests before they became pregnant, or an average of approximately 3 to each.

Use of the Kymograph.—The value of the kymograph in these cases cannot be overestimated. It has been used by me in conjunction with tubal insufflation since May, 1925, and particularly in connection with prognosis and therapy it affords appreciable aid. Of the 590 patients who became gravid, 544 were examined with the kymograph. Thanks to increased experience gained through the use of this instrument, it has been possible to repeat the test both with greater intelligence and with more gratifying results. Forty-nine patients had been insufflated elsewhere.

Tubal Insufflation Followed by Lipiodol Injection.—In 7 of the successful cases with high-grade strictures, lipiodol was also employed. In 3 cases insufflation had been done once before lipiodol was employed; in 3 cases three times and in one case four times. In 4 of these cases insufflation also followed the lipiodol injection, once in 2 cases, four times in one case, and seven times in the other before pregnancy ensued.

The therapeutic efficacy of lipiodol in these 7 cases is difficult to appraise because altogether 29 insufflations had been done before or after the 7 single lipiodol injections. I have had occasion to inject lipiodol in 159 patients and pregnancy followed insufflation and lipiodol in these 7 patients alone. If we omit 99 cases of tubal closure and the 7 cases in which the examination was unsatisfactory, the incidence of pregnancy in the remaining 53 cases is 13.21 per cent. This is less than half the percentage of success where insufflation alone was employed in the general group of patients having tubal strictures (31.13 per cent).

*Rucker²⁵ found that when the tubes were open, pregnancy followed in more than 23 per cent; when partially obstructed, it followed in 20 per cent; and when tighter strictures were present, pregnancy occurred in 33 per cent of his cases. Moench²⁶ observed one pregnancy out of 33 patients with obstructed tubes and 7 pregnancies in 55 cases with open tubes. Baer²⁷ reports 2 cases and Seymour 1 case with high-grade tubal strictures that became gravid after insufflation. In Morgan's²⁸ 8 successful cases, 5 had partial tubal obstructions. In Fuchs' 9 cases, high pressure was required in 6; 3 of these cases became gravid within two weeks, 1 within six weeks, 1 within four weeks, and the sixth became pregnant four months after insufflation. Monbach²⁹ reports 4 pregnancies out of 11 cases with high-grade strictures, and 3 successes out of 14 cases with milder strictures. Francillon-Lobre and Dalsace³⁰ observed 5 pregnancies in 27 cases; 3 of these cases had high-grade strictures.

Radium and X-ray Therapy.—Of the 590 cases of pregnancy, 11 were treated with small doses of radium for delayed and scanty periods and one received a larger dose for menometrorrhagia. Eight of the 12 patients became gravid within one year of the use of radium, 4 within the first six months. Similarly, 29 patients had received x-ray and insufflation therapy before becoming gravid. As all of these patients were insufflated before receiving x-ray or radium therapy, it is difficult to say how much credit for the successful outcome should be allotted to these measures, especially as insufflation of the tubes often intervened between the "stimulating" treatments and pregnancy.

Time of Pregnancy in Relation to Insufflation.—The time elapsing between insufflation and conception was noted. Data were available in 573 cases.

TABLE IX. TIME OF PREGNANCY IN RELATION TO INSUFFLATION

NO. OF PREGNANCIES	TIME AFTER INSUFFLATION
158	Within 1 month
70	Within 2 months
37	Within 3 months
38	Within 4 months
35	Within 5 months
40	Within 6 months
49	Within 2 years
15	Within 3 years
9	Within 4 years
5	Within 5 years
3	Within 6 years
3	Within 7 years
2	Within 8 years
1	Within 10 years

Three hundred and seventy-eight, or 64.07 per cent, of the pregnancies occurred within six months of the test; 108 pregnancies occurred within the second six months.

In 17 cases the time interval was not recorded.

It is noteworthy that 228 patients or 38.64 per cent became gravid within two months after insufflation. This short interval appears to be a fair criterion of the therapeutic value of the method. Many of these patients had been married or sterile five years and longer, a fact which is supportive proof of its efficacy. Obviously, the test cannot be held to have produced a remedial result when more than two regular menstrual periods have intervened between its use and conception except in cases where strictures were encountered. In cases where insufflation has demonstrated normal tubal patency, one can speak only of its diagnostic and prognostic value. The fact that 38 women became gravid in my series after an interval of two years or more following insufflation should cause us to hesitate to give a hopeless prognosis for childbearing when the Fallopian tubes have been found patent or where they have been rendered patent.

The case of L. W. is an example. This 23-year-old woman, sterile for two years, was first seen in 1925. Physical examination was essentially negative except for palpable left adnexa. Repeated uterotubal insufflations indicated nonpatent tubes. The findings at laparotomy in 1929 were: retroverted adherent uterus with several fibroids; right hydrosalpinx with periovarian adhesions; left tube adherent in the pelvis, the fimbriated end how-

ever appearing free. The peritubal and periovarian adhesions were separated, the fibroids were enucleated, the right tube was excised, and the uterus was ventrosuspended. The left tube, before being freed of adhesions, was insufflated through the uninvolved fimbria and showed an obstruction. Retrograde fimbrial insufflation after the left tube was straightened out proved it to be patent down to the uterine end. Three years later, in 1932, she became pregnant and was delivered by cesarean section. In 1941 another pregnancy went to term, and delivery was by cesarean section. At this time the patient at her request was sterilized by tubal excision. Histologic examination of the left tube showed no noteworthy change. The right tubal stump showed chronic salpingitis with decidual reaction of the mucosa.

The Eventuality of Pregnancy.—The data as to the outcome of pregnancy are available in 517 women who became gravid after insufflation in my series. Of these, 419, or 81.04 per cent, had 490 full-term babies; 191 of these were boys, 183 girls, and in 116 the data are lacking. Patients under my own care during pregnancy numbered 254. Of the 250 patients who were personally delivered, 208 or 81.80 per cent had full-term children.

TABLE X. THE EVENTUALITY OF PREGNANCY IN 517 CASES

	NUMBER OF CASES	PERCENTAGE
Term babies only—born alive	383	74.08
Premature babies—born alive	4	.77
Premature and term babies—born alive	4	.77
Premature and incomplete abortions	2	.39
Stillbirth at term	2	.39
Stillbirth	2	.39
Spontaneous abortions	81	15.67
Spontaneous abortions and term babies	26	5.03
Tubal pregnancy—born alive	9	1.74
Tubal and term pregnancies—born alive	4	.77
Total	517	100.00

Many of the patients who aborted belonged to the amenorrhea group. They were not aware of their pregnancy until bleeding began. From my study of these particular women with habitually delayed periods, they appear to exhibit a greater tendency to abort than women with normal menstrual function. On the other hand, the salvage of babies in the cases treated for secondary sterility is particularly striking. Undoubtedly greater care during the pregnancy following therapeutic treatment accounts for the increased number of full-term babies (84 per cent compared to 32 per cent, Table II).

Ninety-four patients who became pregnant following insufflation subsequently encountered renewed difficulty in conceiving. Another insufflation was again succeeded by pregnancy. In 22 of these cases, high-grade strictures were demonstrated by the insufflation preceding the second gravidity.

After an intervening pregnancy the kymographic curve may change, showing some degree of obstruction or improved patency. On the other hand, it may show the same or similar characteristics. Two examples may be cited in this connection:

M. R. was a 26-year-old woman, sterile for almost three years. Physical examination was essentially negative except for the hypoplastic uterus. Repeated uterotubal insufflations indicated uterotubal spasm. During one insufflation performed about two weeks after a

menstrual period, the curve was essentially normal and the tubes were definitely patent. Coitus was advised for that and the next day, and gestation ensued the following month (Fig. 4).

E. E., a patient with secondary sterility, showed evidence of strictured but partially patent tubes at insufflation, Dec. 9, 1929, when the pressure rose to 200 mm. Hg in a somewhat paraboloid curve with a tendency to drop slowly. On repeated insufflation on the same date, pressure rose to 192 mm. Hg with a sharp drop to 38 mm. Hg, without any audible external regurgitation from the cervix. She had a subphrenic pneumoperitoneum and shoulder pains. The patient became pregnant the same month and had a missed abortion six months later. A second insufflation, done Dec. 12, 1930, showed tubal patency at low pressure levels with atypical fluctuations.

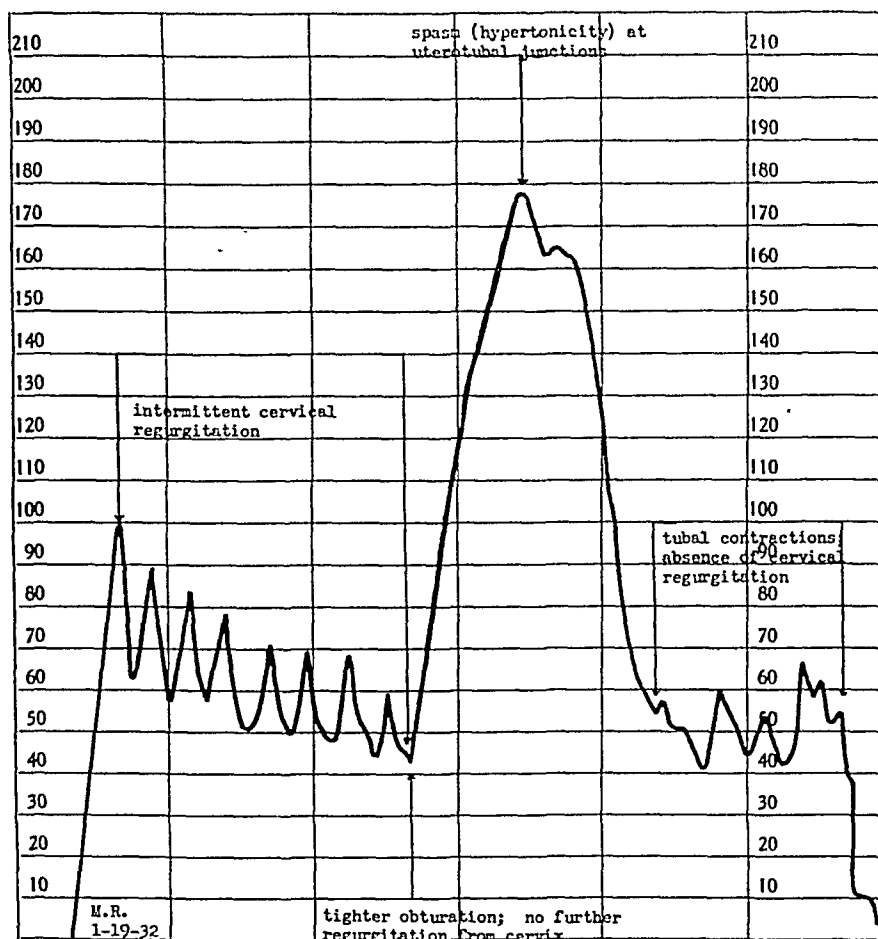


Fig. 4.—Tubograph, Jan. 19, 1932, in case of uterotubal spasm.

The discrepancy in the percentage of successful results obtained by various observers is probably due in general to differences in the cases selected for insufflation, to the possible variations in technique, and to the follow-up of their patients.

To the results already mentioned may be added those of Pribram,³¹ Kaboth,³² Samuel,³³ and Sellheim³⁴ who have concluded that, though the statistical incidence of pregnancy following insufflation cannot be estimated with precision, the method has a value which makes it indispensable in the treatment of sterility. It is not unreasonable to suppose that if the exact outcome of all patients insufflated were known, the sum total of pregnancies would be greater than the reports indicate.

Proof of Therapeutic Efficacy.—If one judges results according to the rigid demands of the criteria for a therapeutic result, we have 26 cases which have fulfilled all the requirements. These 26 cases were women who became pregnant within one month following this procedure. They were over 30 years of age, were sterile for a period of over five years, took no contraceptive precautions for at least one year, and resorted to no other treatment than insufflation. Excluding most of the other cases, there remain 66 in whom a therapeutic action on the part of insufflation is suggested because pregnancy followed upon improvement in the tubal status as a result of repeated insufflations.

In estimating therapeutic results or etiologic factors, the possibility of chance or accident, which must always be taken into account, was seriously considered. In smaller series than the present, chance may have undoubtedly played a large part as it most probably has in a number of my own cases. Ultimate results will naturally vary within certain limits, depending upon special groups of sterility cases and upon the thoroughness with which treatment is carried out. The weight of evidence, all factors considered, points in the larger series of eventuating pregnancies to the fact that, by relieving tubal obstruction, uterotubal insufflation exerts a therapeutic influence in female sterility.

References

1. Giles, A. E.: *Sterility in Women*, London, 1919, Henry Frowde and Hodder & Stroughton, page 101.
2. Peterson, Reuben, and Cron, Roland S.: *J. A. M. A.* 81: 980, 1923.
3. Cron, Roland S.: *J. A. M. A.* 79: 713, 1922.
4. Rongy, Abraham: *AM. J. OBST. & GYNEC.* 3: 553, 1922.
5. Menchikoff, Catherine: *Thèse de la Faculté de Médecine de Paris* 32: 496, 1929.
6. Devraigne, L., and Seguy, Jean: *Médecine* 9: 521, 1928.
7. Coghlan, Cecil: *M. J. Australia* 1: 209, 1930.
8. Hamant, A.: *Rev. franç. de gynéc. et d'obst.* 24: 81, 1929.
9. Floresco, Al., and Naum, Georges: *Gazette Des Hospitaux* 100: 157, 1927.
10. Geppert, F.: *Zentralbl. f. Gynäk.* No. 6, pp. 227-8, Feb., 1924.
11. Rongy, A. J., and Rosenfeld, S. S.: *AM. J. OBST. & GYNEC.* 3: 496, 1922.
12. Sellheim, H.: *Med. Klin.* 19: 1570, 1923.
13. Sellheim, H.: *Deutsche med. Wehnschr.* 56: 859, 1930.
14. Rubin, I. C.: *Am. J. Surg.* 1: 1, 1926.
15. Hirst, J. C., and Mazer, C.: *AM. J. OBST. & GYNEC.* 4: 160, 1922.
16. Pouliot, L.: *J. de méd. et chir. prat.* 99: 809, 1928.
17. Lane-Roberts, C., Sharman, A., Walker, K., and Wiener, B. P.: *Sterility and Impaired Fertility*, London, 1939, Harnish Hamilton Medical Books.
18. Weitzner, G.: *New York State J. Med.* 35: 613, 1935.
19. Abbot, W. F.: *Canad. M. A. J.* 30: 399, 1934.
20. Douay, E.: *Bull. soc. d'obst. et de gynéc.* 16: 361, 1927.
21. Graff, E.: *Monatschr. f. Geburtsch. u. Gynäk.* 62: 159, 1923.
22. Graff, E.: *Die Unfruchtbarkeit Der Frau*, Berlin, 1926, Julius Springer.
23. Davis, H. C.: *Wisconsin M. J.* 22: 256, 1923.
24. Mintz, M. E.: *AM. J. OBST. & GYNEC.* 34: 93, 1937.
25. Rucker, M. P.: *AM. J. OBST. & GYNEC.* 9: 255, 1925.
26. Moench, G. L.: *The Med. Herald and Physiotherapist.* 44: 179, 1925.
27. Baer, J.: *Virginia M. Monthly* 56: 60, 1929.
28. Morgan, T. R.: *Observations on the Rubin Test*, *AM. J. OBST. & GYNEC.* 9: 843, 1925.
29. Mombach, G.: *AM. J. OBST. & GYNEC.* 19: 841, 1930.
30. Francillon-Lobre and Dalsace, J.: *La Gynecologie* 28: 687, 1929.
31. Pribram, E.: *Zentralbl. f. Gynäk.* 48: 2750, 1924.
32. Kaboth, G., and Kleefisch, J.: *Arch. f. Gynäk.* 70: 133, 1929.
33. Samuel, M.: *Therapeutische Fortschritte durch diagnostische Röntgenaufnahmen des Uterus und der Tuben*, *Fortschr. a. d. Geb. d. Röntgenstrahlen* 36: 356, 1927.
34. Sellheim, H.: *Fortschritte in der Sterilitätsbehandlung*, *Prakt. Arzt.* 12: 246, 1927.

SWEAT GLAND TUMORS OF THE VULVA, BENIGN (HIDRADENOMA) AND MALIGNANT (ADENOCARCINOMA)

EMIL NOVAK, M.D., AND R. R. STEVENSON, M.D., BALTIMORE, Md.

(From the Department of Gynecology, Johns Hopkins Medical School)

SWEAT gland tumors have been observed in various parts of the body, perhaps most often in the breast. They are rare, however, and there appears to be no crystallization of opinion among pathologists as to the interpretation of individual cases, or as to the histogenetic problems involved in this tumor group. A glance through any of our modern textbooks on pathology reveals that only a perfunctory and unsatisfying paragraph or two is likely to be devoted to the subject of sweat gland tumors.

The first instance of a tumor for which a sweat gland origin was assumed appears to have been that of Peterson¹ in 1893, the growth involving the skin over the sternal area, although in the case of a small bone tumor reported by Thierfelder² as far back as 1870 a sweat gland origin was at least suspected. Since both these tumors are reported to have contained skin elements, such as hair and sebaceous material, a sweat gland origin seems far less likely than that they were of dermoid nature. These cases, as well as many others, are reviewed by Pick³ in his important contribution of 1904, to which frequent reference will be made in this paper. This author concluded that among the early cases in which a sweat gland origin was assumed only four appeared to be unquestioned. These were the tumors reported by Peterson⁴ in 1892 (not the one alluded to above), Bartel⁵ in 1900, Perthes⁶ in 1903, and Schickele⁷ in 1902.

The case of Schickele is of especial pertinence as regards the immediate subject of the present paper, because it is the only one of the above-mentioned group of four in which the tumor involved the vulva. Schickele's own interpretation of the growth was that it was of mesonephric origin, but a review of his report leaves no doubt as to the correctness of Pick's conclusion that the tumor belongs to the sweat gland group. To the four previously reported cases of genuine sweat gland tumors, Pick adds three of his own, in one of which the tumor was multiple. In all of these the lesions were located in the vulva.

As regards the sweat gland tumors of the vulva, there can be no doubt that these tumors were encountered long before any of the observations reported above, though the real nature of the lesion was either not suspected or at least not established. For example, it is quite certain that a vulvar tumor reported by Werth⁸ as far back as 1878 was of this type, while in the tumor of the labium majus reported by Braun⁹ in 1892 a sweat gland origin was actually suggested by the author, although this case was not in Pick's group of authentic early cases. Again, a very typical case is described by Gebhard¹⁰ in his *Pathologische Anatomie des Weiblichen Sexualorgane* (1899), but the author expressed himself as totally at a loss as to its origin.

Pick's exhaustive paper established beyond doubt the sweat gland origin of certain vulvar lesions, and it included also an accurate description of the

histological characteristics of these growths. In his description Pick repeatedly stressed the double layer of cells present in some sweat glands, and also in the acini of these tumors. Again, he called attention to the layer of "ectodermal muscle cells" seen between the epithelium and the membrana propria of certain sweat glands, and also in every one of the vulvar tumors described by Pick. This myoepithelial layer had been described by von Koelliker¹¹ as far back as 1889. He mentioned, however, that not all of the sweat glands show these elements, and he quotes Rabi¹² as stating that certain sweat glands in the axillary and scalp areas show three or even four layers of epithelial cells. Moreover, he calls attention to the fact that Perthes in the description of his case noted that secretory products, not merely degenerative, were found in some gland lumina.

Types of Sweat Glands.—These facts are noted simply because they indicate a growing realization of the fact that sweat glands are not all alike histologically, and probably not embryologically or functionally as well. The sweat glands were first described by Purkinje in 1833, the sebaceous glands by Eichhorn some years earlier, in 1826. Even at the present day, it is quite certain that the prevalent concept of the skin glands is that they are quite sharply divisible into these two groups, the acinous sebaceous glands secreting the characteristic sebaceous material and the tubular sweat glands the watery sweat. This, however, is not the case, for all sorts of intergrades have been noted, both histological and functional. In 1879 Graff¹³ showed that the secretion of certain of the tubular glands contains fatty material, while Ranvier¹⁴ described the presence of desquamated gland cells in the secretion of certain glands. A thorough review of these and many other similar observations is given by Hoepke,¹⁵ to whose article the interested reader may be referred.

On the basis of such observations, we can no longer think of the sweat glands as having a stereotyped structure or function, and they can now be subdivided into several varieties. Various groupings were described by the early workers in this field, such as Schiefferdecker¹⁶ and Schaeffer.¹⁷ However, the simplest and most serviceable subdivision would appear to be into three groups, as given by Maximoff.¹⁸ Those in which the epithelial gland cells remain intact during the secretory process are designated as merocrine glands. Those in which the secretion includes extruded portions of the cytoplasm of the cells are spoken of as the apocrine glands, and their distribution appears to be limited to certain areas of the body. These include the axillae, the nipple area, the mons pubis, the abdominal walls, the groins, the labia majora, and the perineum (Hoepke). They are always associated with hair follicles. This is of interest, since the sebaceous glands, perhaps more traditionally associated with the hair follicles, are also found in hair-free regions of the body, such as the labia minora, the glans and prepuce, the oral cavity and lips (Hoepke).

A third group of glands is the holocrine, in which the lining epithelial cells degenerate completely and make up the gland secretion, as in the case of the sebaceous and mammary glands. None of the ordinary sweat glands of the body, however, are of this type.

From what has already been said, as well as from other observations which could be adduced, there is ample justification for the statement, previously made, that all sorts of histological and functional gradations are to be noted in the sweat glands, and the question arises as to whether any of these varieties is more prone to neoplastic growth than others.

We know of no data on this point as applied to sweat gland tumors of other parts of the body, but as regards the vulva there is some evidence to indicate that it is the apocrine group of glands which are most likely to give origin to the sweat gland tumors of this region. With some reported cases the assumption of such an origin seems justified, with others not so clear, and it is probable that the assumption of an apocrine gland origin for practically all these tumors has been overaccentuated. It was apparently McDonald¹⁹ who suggested this explanation, and it undoubtedly applies to some cases. However, the structure of different sweat gland tumors of the vulva shows considerable variation, and the classical original paper of Pick took cognizance of these variations in structure.

Types of Benign Sweat Gland Tumors.—Pick set forth also a nomenclature based on variations in histogenesis. He applied the designation of hidradenoma to those tumors which arise from mature sweat glands, and that of adenoma hidradenoides to those which arise from immature or undifferentiated sweat glands, or from the surface epithelium itself. The latter concept is in line with the view of Krompecher²⁰ that the basal cells of the skin epithelium may give rise to either sebaceous or sweat gland tumors, although not all dermatological pathologists accept this view. Pick described also a third variety characterized by marked papilliferous tendencies, and to this he applies the designation of hidrocystadenoma papilliferum. Moreover, Meyer²¹ has called attention to the fact that in some vulvar lesions one deals merely with adenoma-like proliferations of the sweat glands rather than with genuine adenoma. Our Case 11 appears to belong to this category.

All these subdivisions are confusing. In some tumors the histological study will probably justify one or other of the designations mentioned above, but in others there is sure to be uncertainty on this point. It is probable that the average gynecologic pathologist will prefer to include all genuine sweat gland adenomas, regardless of precise mechanisms of histogenesis, as hidradenoma. There would seem to be no objection to this, since the term hidradenoma is a fairly inclusive one, embracing all adenomatous tumors of sweat gland origin.

Similar uncertainty must often exist as to whether or not the tumor arises from apocrine glands. Circumstantial but not conclusive evidence may be furnished by the presence of apocrine glands adjoining the lesion. However, it is not always easy for the gynecologic pathologist, inexperienced as he is likely to be in these dermatological niceties, to differentiate the apocrine from the merocrine glands, especially since intermediary histological types exist. The former are apt to be somewhat larger and less tortuous, the myoepithelial layer is apt to be more highly developed, and the epithelial cells may show the protrusions which precede the cytoplasmic extrusion, while cast-off



Fig. 1.—Apocrine gland "pad" from axilla of gorilla. Note, especially near the center, the rather streaky appearance produced by tangential section through the myoepithelial layer. (Courtesy of Dr. W. T. Strauss, Carnegie Institute of Embryology.)



Fig. 2.—A sweat-gland tumor from the scalp, showing the double epithelial layer so often found in sweat gland tumors. The pale tuft-like appearance of the epithelium, seen especially in the upper portion of the section, suggests an apocrine origin.

cytoplasmic and at times nuclear material may be found within the lumina. The epithelial layer has a tendency to draw away from the basement membrane. There are other differences which have been described, but the distinction is not always easy. Dr. Wm. T. Strauss of the Carnegie Institute tells us that, in primates like the gorilla, large collections of apocrine glands, or apocrine "pads" occur in the axilla as well as in certain other areas. (Figs. 1 and 2.)

Clinical Characteristics.—Hidradenoma of the vulva has been noted at various age periods, but not, so far as we know, in very young individuals. The



Fig. 3.—Case 1. (Gyn. Path. 2863.) A small vulvar nodule in the fold between the left labium minus and majus, in a patient of 40 years. The section is a poor one, dating from the early days of the laboratory (Oct. 13, 1898).



Fig. 4.—Case 2. (Gyn. Path. 10525.) A nodule from the right labium majus, showing a typical intracystic papillary structure. The glands in the wall appear to be of merocrine rather than apocrine type.

youngest patient in our series was 28 years, the oldest 67 years. The most common location of the lesion is on the labia majora, and next most common in the paralabial skin or perineum. In a few cases, as in one of our own, one of Schickele, and one of Eichenberg,²² the growth has been situated on the



Fig. 5.—Case 3. (Gyn. Path. 42177.) A small, well-encapsulated nodule from the labium minus of a patient of 67 years. Its diameter was 1 cm. Most of the glands suggest the apocrine type. Removed incidentally to plastic operation. (Private patient of Dr. Emil Novak.)



Fig. 6.—Case 4. (Gyn. Path. 44563.) The tumor formed a small nodule in the right labium majus. The patient, age 36, was pregnant at 3 months. Because of apprehensiveness as to possible malignancy, the right inguinal glands were excised, but no metastasis found, and the patient remained well. (Private patient of Dr. E. H. Richardson.)

labium minus. This is of interest since many histologists believe that sweat glands are not normally found in the lesser labia. This may be true of the ordinary sweat glands, but one cannot be so sure as to glands of the apocrine type, which are rather closely related to sebaceous glands, of which there are

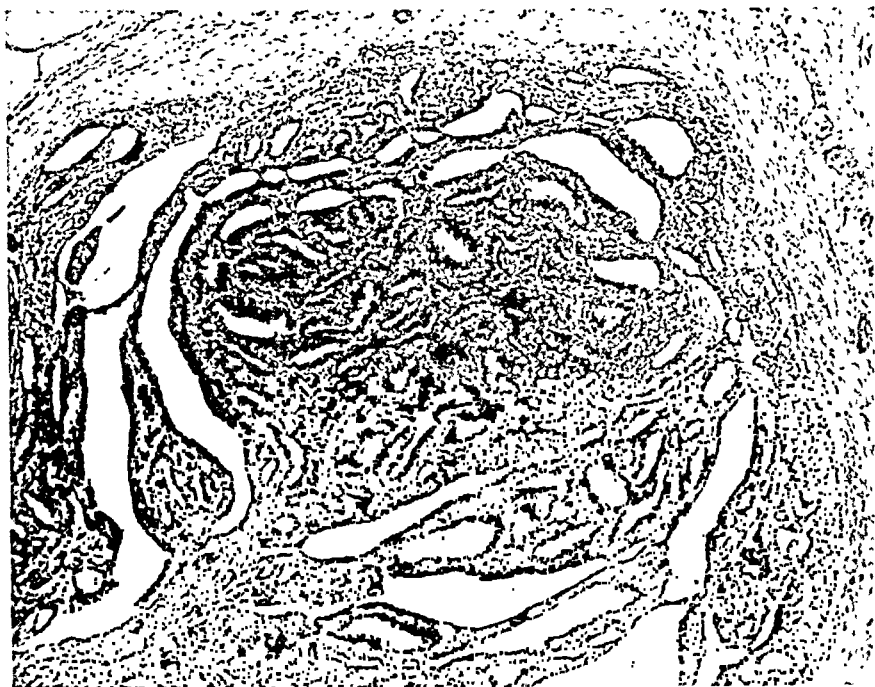


Fig. 7.—Case 5. (Gyn. Path. 45958.) A nodule from the left labium minus in a patient of 37 years. (Private patient of Dr. H. S. Everett.)

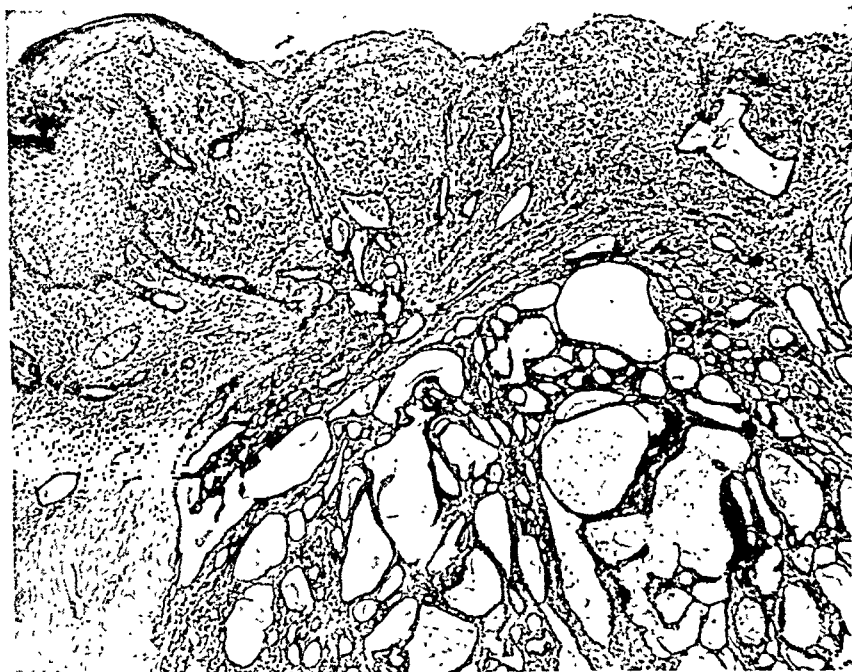


Fig. 8.—Case 6. (Gyn. Path. 47180.) A nodule the size of a cherry in left labium minus, resembling a fibroma, but with rather reddish hue to the overlying skin. The patient was 55 years of age. The picture in this case is that of a loosely adenomatous growth, with superficial ulceration of the overlying skin. (Private patient of Dr. Emil Novak.)

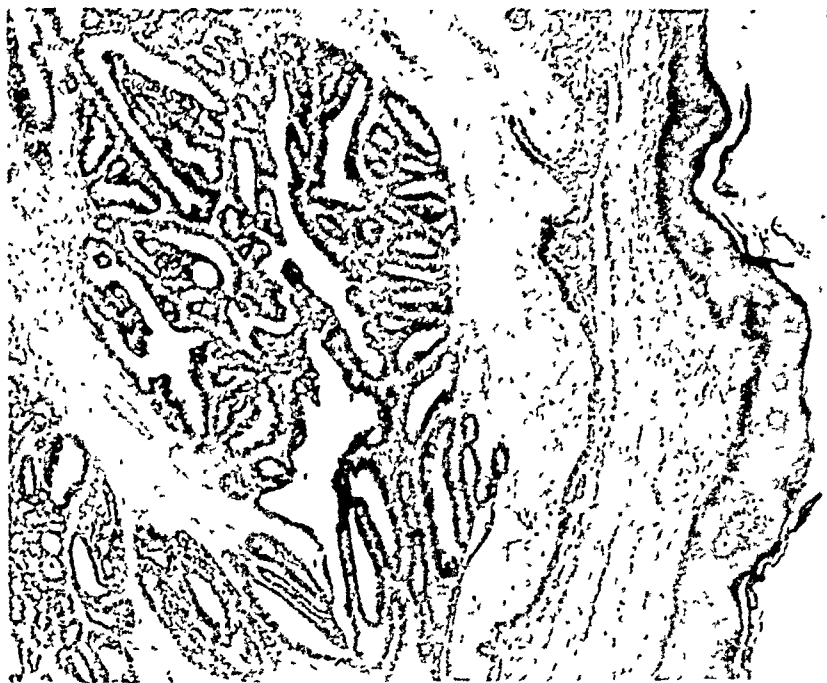


Fig. 9.—Case 7. (Gyn. Path. 51053.) A nodule $1\frac{1}{2}$ cm. in diameter in left labium majus. Patient was 37 years of age. Note the stratification of the epithelium just below the skin. (Private patient of Dr. Emil Novak.)



Fig. 10.—Case 8. (Gyn. Path. 54045.) A small vulvar nodule from a patient of 39 years. The glands in the vicinity of the nodule are not of apocrine type. (Private patient of Dr. Leo Brady.)



Fig. 11.—Case 9. (Gyn. Path. 56523.) A small cystic nodule in labium majus, from a patient of 28 years. Just above the hidradenoma can be seen a large dilated apocrine gland. (Private patient of Dr. H. S. Everett.)



Fig. 12.—Lower-power of another section from Case 9, showing the extrusion of the papillary growth through the skin defect.



Fig. 13.—Case 10. (Gyn. Path. 58078.) A small, subcutaneous vulvar nodule in a patient of 52 years. The adjacent glands do not appear to be of apocrine type. (Private patient of Dr. L. R. Wharton.)



Fig. 14.—Case 11. (Gyn. Path. 60913.) A nodule appearing clinically like a small fibroma in a patient of 46 years. The structure is not like that of a typical hidradenoma, suggesting simply a hyperplastic increase of apocrine glands. Since it formed a definite neoplastic nodule, the case has been included as a benign sweat gland tumor. (Private patient of Dr. Leo Brady.)



Fig. 15.—Case 12. (Gyn. Path. 66068.) A small reddish nodule on the left labium minus, in a patient of 61 years. Pressure over nodule caused exudate of pulpy, reddish-brown material. The section shows the intracystic papillary pattern seen in many hidradenomas, and also the extrusion of papillary material through the skin opening. (Private patient of Dr. Emil Novak.)

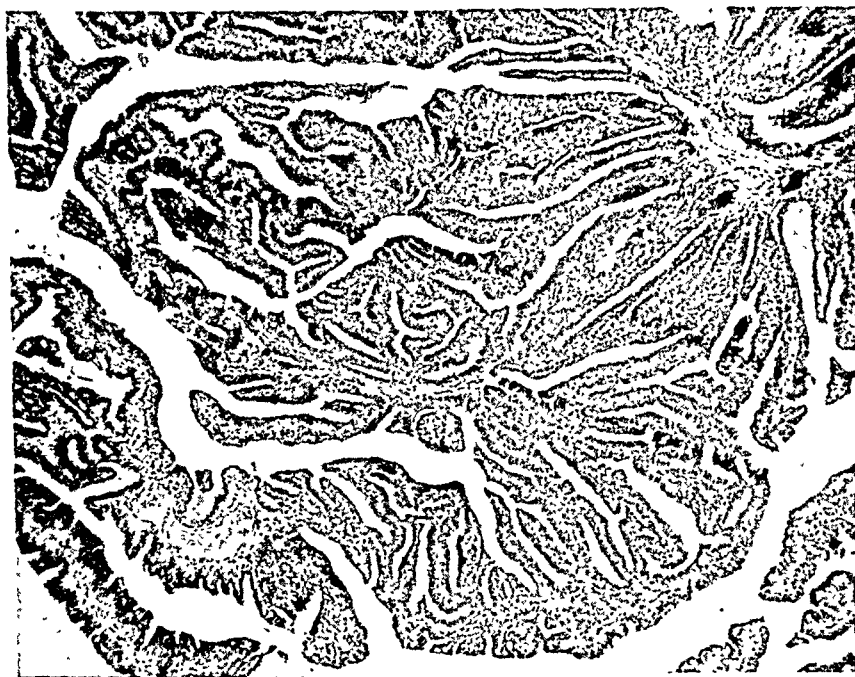


Fig. 16.—Case 13. (Gyn. Path. 62373.) A small rounded sessile nodule 1 cm. in diameter in the vestibule, 1 cm. to right of midline and $1\frac{1}{2}$ cm. posterior to the glans clitoridis. No other hidradenoma has been reported as situated in the vestibular area. The patient was 45 years of age. (Private patient of Dr. Emil Novak.)

enormous numbers in the labia minora. There appears to be no precise knowledge on this point, and perhaps the sweat glands from which hidradenoma develops in this region are to be interpreted as aberrant or misplaced.

In our most recent case, observed in a private patient of the senior author, the location of the tumor was in the anterior position of the vestibule, about 1 cm. to the right, and $1\frac{1}{2}$ cm. anterior to the glans clitoridis. So far as we know, no other hidradenoma has been observed in this region, and yet it was quite typical, as can be seen from Fig. 16. Clinically, it presented as a raised, sessile, rounded nodule, 1 cm. in diameter, with a tiny abrasion-like reddish area at its summit, so that a presumptive diagnosis of hidradenoma was made before excision of the nodule.



Fig. 17.—Case 14. (Gyn. Path. 62662.) A nodule 2 cm. in diameter, slightly elevated, in perineal body just behind right labium majus (see Fig. 18). (Private patient of Dr. R. W. Te Linde.)

It is of interest to note that all of our fifteen cases of hidradenoma occurred in white patients, and not a single one in Negro women, in spite of the fact that such a large proportion of our clinic patients are Negroes. This is all the more surprising since Homma²³ has shown that the apocrine glands, which have been thought to be the common source of hidradenomas, are three times as numerous in Negroes as in whites.

The gross appearance of the lesion varies. It is always small, rarely reaching a size larger than that of a cherry, and usually not over 1 cm. in diameter. It may present as a small, firm, subcutaneous nodule, like a small skin fibroma, covered by intact skin. In other cases it is soft, resembling a small sebaceous cyst, for which it is commonly mistaken. Not infrequently there is a small superficial granular area on the surface. If pressure is made on the small nodule, one is apt to be surprised by the fact that, instead of a

typical sebaceous exudate, the material expressed is reddish-brown and pulpy. This should at once suggest the real nature of the lesion. There is no pain, and often no tenderness or soreness, especially when the skin surface is intact, and the nodule is ordinarily quite movable. In a considerable number of cases the patient herself has not noticed the nodule, its removal being incidental to vaginal operative procedures.

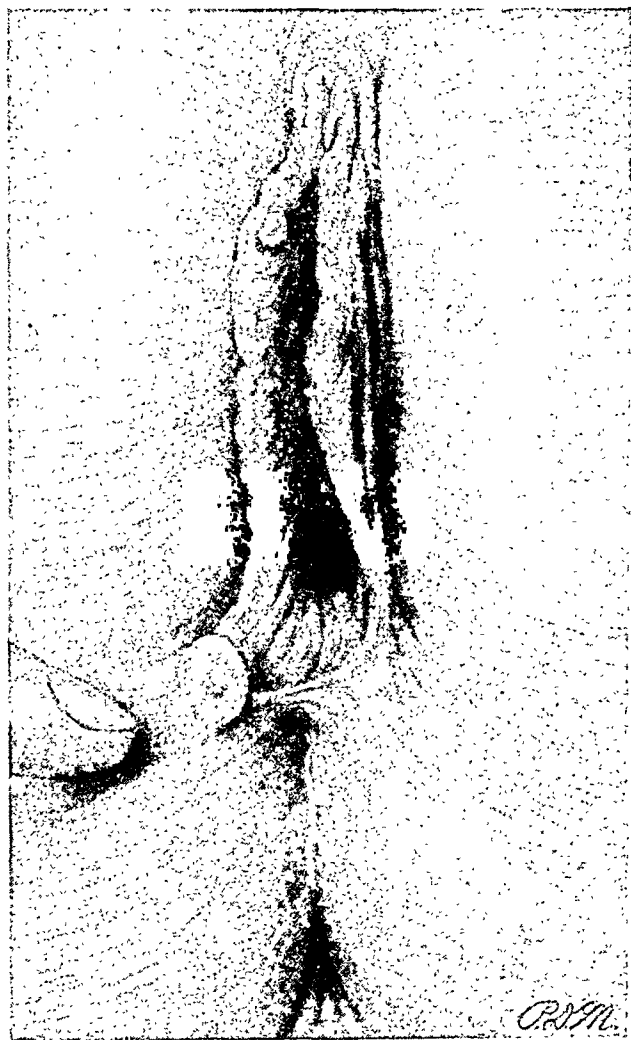


Fig. 18.—Gross appearance in Case 14. (Kindness of Dr. R. W. Te Linde, from forthcoming book on *Operative Gynecology*.)

Microscopic Characteristics.—There is considerable variation in the microscopic appearance of these hidradenomas, as might be inferred from what has already been said. In the most common variety, the pattern is of intricate adenomatous type, some of the glands being small and closely packed, others large and cystic. The epithelium in many, but not by any means all of the glands, shows an inner short columnar or cuboidal layer, and beneath this a layer of the rather closely packed small dark nuclei of the myoepithelium. The latter, however, is frequently absent.

On the other hand, there is a frequent tendency to proliferation and stratification of the epithelium, so that some of the smaller lumina may be com-

pletely filled. Even patches of pavement epithelium may be seen, not unlike the squamous plaques seen in cervical epidermidization, and Schiffmann²⁴ described small epithelial pearls which he thought might indicate malignancy. These epithelial proliferative changes might well in other locations lead to this suspicion, but they are much less significant in these sweat gland tumors which are essentially normal in appearance, and these may be of either the merocrine or apocrine types. In a number of our own cases, collections of essentially normal glands, often clearly of apocrine variety, are seen side by side with areas of involved tubular pattern in which the sharply defined epithelium is strikingly different from the rather large pale cells, with small nuclei, which line the apocrine glands. It seems a fair assumption that such tumors are not of apocrine gland origin, but, on the other hand, such pictures would suggest also that the epithelium of the tumor may undergo a considerable degree of transformation or dedifferentiation. In other tumors the original apocrine epithelial characteristics seem to be retained, so that even in areas where there has been much proliferation, the tufts of epithelium often produced may be composed of the large, pale, and perhaps indistinctly marked epithelial cells suggestive of apocrine histogenesis.



Fig. 19.—Case 15. (Gyn. Path. 62960.) A small, reddish-purple growth from the left labium, just anterior to the position of Bartholin's gland. Patient was 47 years of age. (Private patient of Dr. Leo Brady.)

In other tumors the tubules are small and narrow, arranged in a zigzag fashion, and all lined by low, sharply differentiated epithelium, with perhaps sweat glands of the ordinary nonapocrine variety in the vicinity. In such cases it would seem farfetched and probably incorrect to invoke an apocrine gland origin. We cannot insist on any of these finer distinctions, but it does seem to us that the available evidence does not justify the assumption that hidradenoma is always of apocrine gland origin.

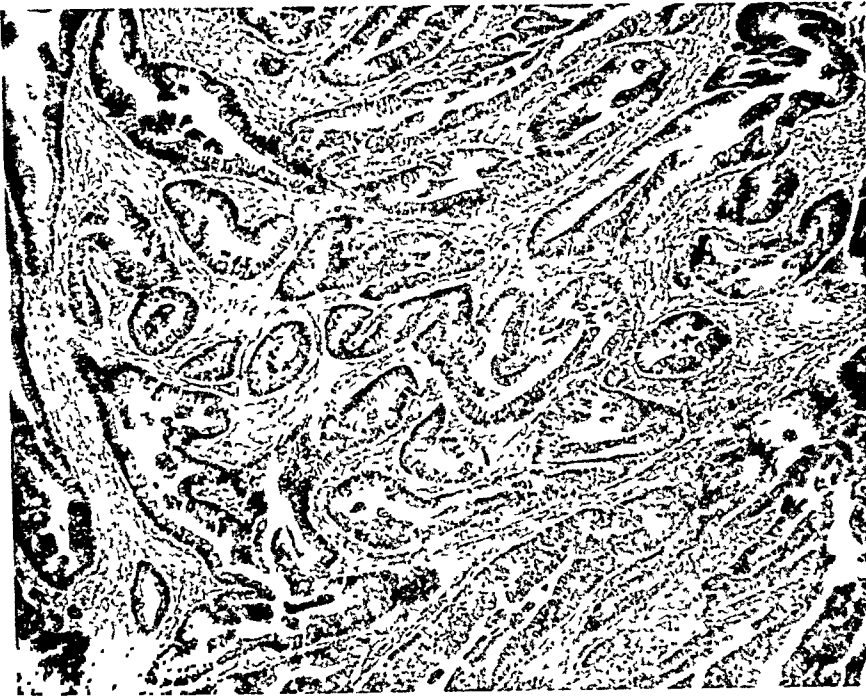


Fig. 20.—Case 16. (Gyn. Path. 33437.) Apparently primary adenocarcinoma of vulva, the lesion involving almost the whole vulva, but not Bartholin glands. The patient was 60 years of age. There was no evidence of any other possibly primary site. Treatment was palliative and the patient died about two months after being seen. A sweat gland origin is possible, but cannot be assumed.



Fig. 21.—Case 17. (Gyn. Path. 33613.) Another apparently primary and highly undifferentiated adenocarcinoma of vulva, presenting as a large, indurated, ulcerative lesion of the posterior part of the left labium majus, in a patient of 41 years. A radical operation was done, but the patient died one year after operation. Here again a sweat gland origin is possible, but not by any means certain.

The Question of Malignancy.—From what has been said as to the microscopic pictures presented by these sweat gland tumors, it is easy to see how they can be readily mistaken for adenocarcinomas. This would apply especially to the highly papilliferous variety. Such an error in diagnosis would be natural enough if one did not know the source of the lesion. For example, Aschheim²⁵ mentions a case in which he examined sections of what he thought was a biopsied cervix, and in which he made a diagnosis of adenocarcinoma. He learned later that the lesion was from the vulva, and revised his diagnosis to that of benign hidradenoma. He agrees that hidradenoma is to be looked upon as benign, and expresses doubt as to the supposed malignancy in the case of Ruge, which will be mentioned in the next paragraph.

Throughout the entire literature of the subject there is constant emphasis on the absence of any suggestion of clinical malignancy, and also constant reference to one or more of four cases in the literature which have been reported as malignant. We have carefully reviewed the original reports of these four cases, and conclude that in only one of them does there seem to be valid evidence for the assumption of malignancy. The first of this group was reported by Ruge²⁶ in 1905 under the designation of "Schweissdrüsenkarzinoma." The histological description and the illustrations depict a tumor identical with all the other benign hidradenomas which have been reported, and there is nothing in the report to suggest clinical malignancy of the lesion which was cured by simple excision.

The sweat gland epithelium appears to be prone to this rather pleomorphic proliferative activity. Mitoses, on the other hand, are seen only infrequently.

Even in cases in which the pattern is highly pseudomalignant, one not infrequently finds areas of sweat glands.

The second case which has been quoted by various authors as possibly malignant is that of Schiffmann,²⁴ in 1920. This likewise was a clinically benign nodule of the labium majus observed in a patient 40 years of age, and treated by simple excision. In the microscopic description Schiffmann mentioned that in addition to the usual features a number of small epithelial pearls were seen in certain areas, although otherwise the tumor was typical enough. He rather naively suggests that the term adenoma malignum might be applied to lesions in which the pathologist is in doubt as to whether they are benign or malignant. He compromises by calling his tumor an adenocarcinoid. However, it was clinically benign and resembles many of the other clinically benign cases reported except for the so-called pearls. The latter, however, are not to be considered as suggesting malignancy, for reasons which have been already discussed.

Another case sometimes quoted is that of Burg²⁷ (1930), but a reading of his paper shows that he considered it to be clearly benign, classifying it as adenoma hidradenoides. For that matter he expressed doubt as to the supposed histological malignancy of the cases of Ruge and Schiffmann. So far as we can see, the only reason that some authors have included this case in the supposedly malignant group is Burg's remark that the material expressed from the nodule before excision had led him to suspect possible malignancy.

Finally, reference must be made to the paper of Eichenberg²² (1934), from material studied in the laboratory of Robert Meyer. Twelve cases of typical hidradenoma were reported, all cured by excision. In one of these, a small local recurrence was noted, requiring further excision, but this Eichenberg himself says was obviously due to the incompleteness of the first excision.

In the course of his paper, however, Eichenberg mentions another case of vulvar tumor, also thought to be definitely of sweat gland origin, in which the histological picture was quite different. Unfortunately, there are no illustrations of the microscopic appearance, but the author emphasizes the extreme degree of epithelial proliferation and the invasion of surrounding tissue by cell columns and tubules. Meyer interpreted this tumor as an adenocarcinoma arising secondarily in a hidradenoma. As to its clinical malignancy, there is little doubt. It was described as an almond-sized nodule in the left labium majus, which was widely extirpated with the growth, together with the left inguinal glands, which showed definite metastasis. There had been no recurrence two years after operation.

It will thus be seen that only a single case in the literature can be properly considered as malignant from a clinical standpoint. It is surprising therefore that Folsome,²⁸ so recently as 1940, stated that 27 per cent of cases were locally invasive and presumably malignant, and we cannot imagine the basis for this statement.

Even more unfortunate is the fact that in a very recent report, that of McDonald, Lovelady and Waugh,²⁹ a large group of vulvar sweat gland tumors is reported under the designation of adenocarcinoma of the vulva. Thirty of these, on the basis of the clinical and histological description and the accompanying illustrations, belong to the benign hidradenoma group. The other two appear to be malignant tumors of unknown histogenesis, nothing in the descriptions suggesting that they are of sweat gland origin, although this possibility cannot be ruled out. With reference to the larger group of thirty sweat gland tumors, the authors emphasize their clinically benign nature, stating that in every instance simple excision effected cure. In other words their designation of the tumors as papillary adenocarcinomas was based entirely upon their interpretation of the local histology.

Granting the superficial resemblance of some hidradenomas to adenocarcinoma, the illustrations accompanying this paper leave no doubt as to the hidradenomatous nature of the depicted lesions and would not seem to justify even a histological diagnosis of adenocarcinoma, if one is familiar with the frequent stratification and the frequent papilliferous ingrowths which characterize clinically benign tumors of sweat glands in this region. The term adenocarcinoma certainly conveys the idea of clinical malignancy, and it would seem incredible, if the tumors were really adenocarcinomas, that clinical malignancy and metastasis would not have been observed in at least some of this rather large group of cases. This is especially true in view of the strong propensity of vulvar carcinoma in general to metastasize rather early in its course. In view of these facts, we believe that a disservice has been done by these authors in thus flat-footedly designating these tumors as adenocarcinomas.

This is not to say that genuine adenocarcinoma cannot have a sweat gland origin, as would seem to be attested by the case of Eichenberg,²² described above. Even in the latter, the histological picture differs from that of the papilliferous but clinically benign hidradenomas only in degree. Epithelial proliferation even in the latter may be pronounced and plaques of horny epithelium may be seen, producing pictures which, in other organs like the uterus or ovary, would incline one to the diagnosis of malignancy.

The practical lesson, on the basis of all past experience with these vulvar growths, is that such histological features often characterize entirely benign lesions of sweat gland origin, but that, in spite of this fact, one should not treat these growths too lightly. When they are small and slow growing or quiescent, as practically all reported cases have been, simple but complete excision suffices to effect cure. It is always advisable, however, especially in the case of lesions showing a high degree of epithelial proliferation and a markedly papilliferous pattern, to keep the patients under observation. This seems like a wise precaution in spite of the fact that in only one case in the literature has malignancy appeared to develop in a hidradenoma. Even this assumption may not be correct, as the tumor may have been definitely malignant from the beginning. In other words, the sweat glands may be the seat of origin of adenocarcinoma just as they may be of the benign hidradenoma, and not necessarily with the intermediation of the latter.

Possible Sweat Gland Origin of Some Primary Vulvar Adenocarcinomas.—Primary adenocarcinoma of the vulva is exceedingly rare, and when it does occur, one can usually do little more than speculate as to its origin. From this statement we can perhaps except carcinoma of Bartholin's gland, as the location of the tumor in such cases will usually be helpful in indicating its source. Other possible sources would be vestigial mesonephric (Wolffian) structures, vulvar endometriosis, and aberrant breast tissue, of which a number of cases have been reported. In addition to these, one must also think of the possibility of sweat gland origin. We have observed two instances of primary adenocarcinoma in which a sweat gland origin was thought to be probable, but certainly not established beyond doubt (Figs. 20 and 21). Other cases of this "probable" type have been reported by McDonald and his co-workers,²⁹ but the fact remains that this is still a rather vaguely defined entity.

Instead of giving detailed reports of the fifteen cases of hidradenoma which we have observed, the essential data are included in the self-explanatory legends of the photomicrographs of each of these tumors. We may simply add that all these tumors were treated by simple excision, and no recurrence was noted in any case.

Summary

The sweat gland tumors of the vulva constitute a relatively rare but highly interesting group. Clinically they present as small and innocent-looking growths on or near the vulva, but to one not familiar with their histological appearance the microscopic picture is apt to be rather startling, and perhaps to lead to the diagnosis of adenocarcinoma. However, in only one case in the litera-

ture, that of Eichenberg, has there been apparently unimpeachable evidence of malignant change, both clinical and microscopic. All other cases, including the fifteen cases reported herewith, have been clinically benign and all have been cured by simple excision.

Granted that the characteristic microscopic picture of these growths might well in other tissues lead to the diagnosis of adenocarcinoma, there would seem to be no justification for applying the term adenocarcinoma to these notoriously benign sweat gland tumors. It is entirely possible, and perhaps even probable, that some instances of the rare primary adenocarcinoma of the vulva may be of sweat gland origin, as in the two cases of this group we have included in this paper. Such an origin, however, is difficult to establish. The histogenesis of these sweat gland tumors has been thoroughly discussed in our paper, and the suggestion made that the apocrine gland derivation of these growths has probably been overaccentuated, though our knowledge on this point is still very incomplete. The clinical and microscopic characteristics of hidradenoma have likewise been rather fully discussed in the paper.

References

1. Peterson, W.: *Arch. f. Dermat. u. Syph.* 25: 442, 1893.
2. Thierfelder, F. A.: *Arch. f. Heilkunde* 11: 401, 1870.
3. Pick, L.: *Virchows Arch. f. path. Anat.* 175: 312, 1904.
4. Peterson, W.: *Arch. f. Dermat. u. Syph.* 24: 1892, 1893.
5. Bartel, J.: *Ztschr. f. Heilk.* 21: 200, 1900.
6. Perthes, G.: *Deutsche Ztschr. f. Chir.* 65: 283, 1903.
7. Schickele, G.: *Beitr. z. Geburtsh. u. Gynäk.* 6: 449, 1902.
8. Werth, R.: *Zentralbl. f. Gynäk.* 2: 513, 1878.
9. Braun, H.: *Arch. f. klin. Chir.* 43: 213, 1892.
10. Gebhard, C.: *Pathologische Anatomie des weiblichen Sexualorgane*, Leipzig, 1899, p. 591.
11. von Koelliker, R. A.: *Handbuch d. Gewebslehre d. Menschen* f. Auflage Bd. 1, Leipzig, 1889.
12. Rabl, H.: *Histologie der normalen Haut des Menschen*, vol. 1, p. 109, in *Handbuch d. Hautkrankh.* of Fr. Macek. Wien, 1901.
13. Graff. Quoted by Hoepke.¹⁵
14. Ranvier: Quoted by Hoepke.¹⁵
15. Hoepke, H.: *Die Haut*. Part 1, Vol. 3 of Wilhelm v. Mollendorff, *Handbuch der mikroskopische Anatomie des Menschen*, Julius Springer, Berlin, 1927.
16. Schiefferdecker, P.: *Arch. f. Anat. u. Physiol.* 1913. Quoted by Hoepke.¹⁵
17. Schaeffer, J.: *Anat. Anz.* 57: 242, 1923.
18. Maximoff, A. A.: *Textbook of Histology*, ed. 3, Philadelphia, 1938, W. B. Saunders Co., p. 285.
19. McDonald, J. R.: *Am. J. Clin. Path.* 11: 890, 1941.
20. Krompecher: Quoted by Meyer.²¹
21. Meyer, R.: *Ztschr. f. Geburtsh. u. Gynäk.* 86: 420, 1923.
22. Eichenberg, H. E.: *Ztschr. f. Geburtsh. u. Gynäk.* 109: 358, 1934.
23. Homma, H.: *Bull. Johns Hopkins Hosp.* 38: 365, 1926.
24. Schiffmann, J.: *Zentralbl. f. Gynäk.* 44: 59, 1920.
25. Aschheim, S.: *Ztschr. f. Geburtsh. u. Gynäk.* 86: 417, 1923.
26. Ruge, H.: *Ztschr. f. Geburtsh. u. Gynäk.* 56: 307, 1905.
27. Burg, E.: *Zentralbl. f. Gynäk.* 54: 395, 1930.
28. Folsome, C. E.: *J. A. M. A.* 114: 1499, 1940.
29. McDonald, J. R., Lovelady, S. B., and Waugh, J. M.: *AM. J. OBST. & GYNEC.* 42: 304, 1941.

TEN YEARS OF CESAREAN SECTION AT THE BOSTON LYING-IN HOSPITAL*

FREDERICK C. IRVING, M.D., BOSTON, MASS.

(From the Department of Obstetrics, Harvard Medical School, and the Boston Lying-in Hospital)

THIS report covers the 1,887 consecutive cesarean sections performed at the Boston Lying-In Hospital during the ten years from 1934 to 1943 inclusive. One thousand ninety-four, or 58 per cent of these operations, were on patients admitted to the public wards; 793, or 42 per cent, were on private patients. All public ward patients are on the teaching service of Harvard Medical School, and those delivered by cesarean section were operated on by the visiting obstetricians, the resident obstetricians, and the house-officers; such patients are under the direction of the chief of staff of the hospital, and the policies governing their treatment are determined by him in consultation with the other members of the visiting staff. Operations on the private patients are performed by the visiting staff and by the courtesy staff, which consists of selected graduates of the Boston Lying-In Hospital. Policies governing the treatment of private patients are left largely to the individual obstetricians.

Fig. 1 compares the results obtained during this ten-year period with cesarean section after viability and with methods of pelvic delivery in the case of the public ward patients only, who were selected because their records were readily available. This chart shows: (1) Normal delivery was fifteen times safer for the mother than cesarean section and over two and one-half times safer for the infant. (2) Low forceps were seven and one-half times safer for the mother than cesarean section and just as safe for the infant as normal delivery. (3) Other things being equal, cesarean section is not a substitute for either low-forceps or normal delivery. (4) On the other hand, midforceps was almost as dangerous for the mother as cesarean section and about eight times more dangerous for the infant. (5) Provided it is indicated, therefore, cesarean section compares favorably with midforceps as a method of delivery.

In studying these 1,887 cesarean sections, four questions are raised: (1) Was this operation employed too frequently, i.e., was it substituted for either normal delivery or low forceps in cases where either of these simple methods of delivery might have been employed? (2) What were the causes of maternal and fetal deaths in cesarean section? Might some of these deaths been avoided, and if so, how? (3) How did the results with private and public patients compare? (4) How did they compare with those reported in other series of similar magnitude? These questions may be answered by considering the following topics: (1) incidence; (2) the operators; (3) indications; (4) special diagnostic

Read by invitation before the Cincinnati Academy of Medicine, Dec. 19, 1944.

and therapeutic measures; (5) morbidity; (6) fetal mortality; (7) maternal mortality; (8) cesarean section as a method of delivery in certain complications of pregnancy and labor other than dystocia.

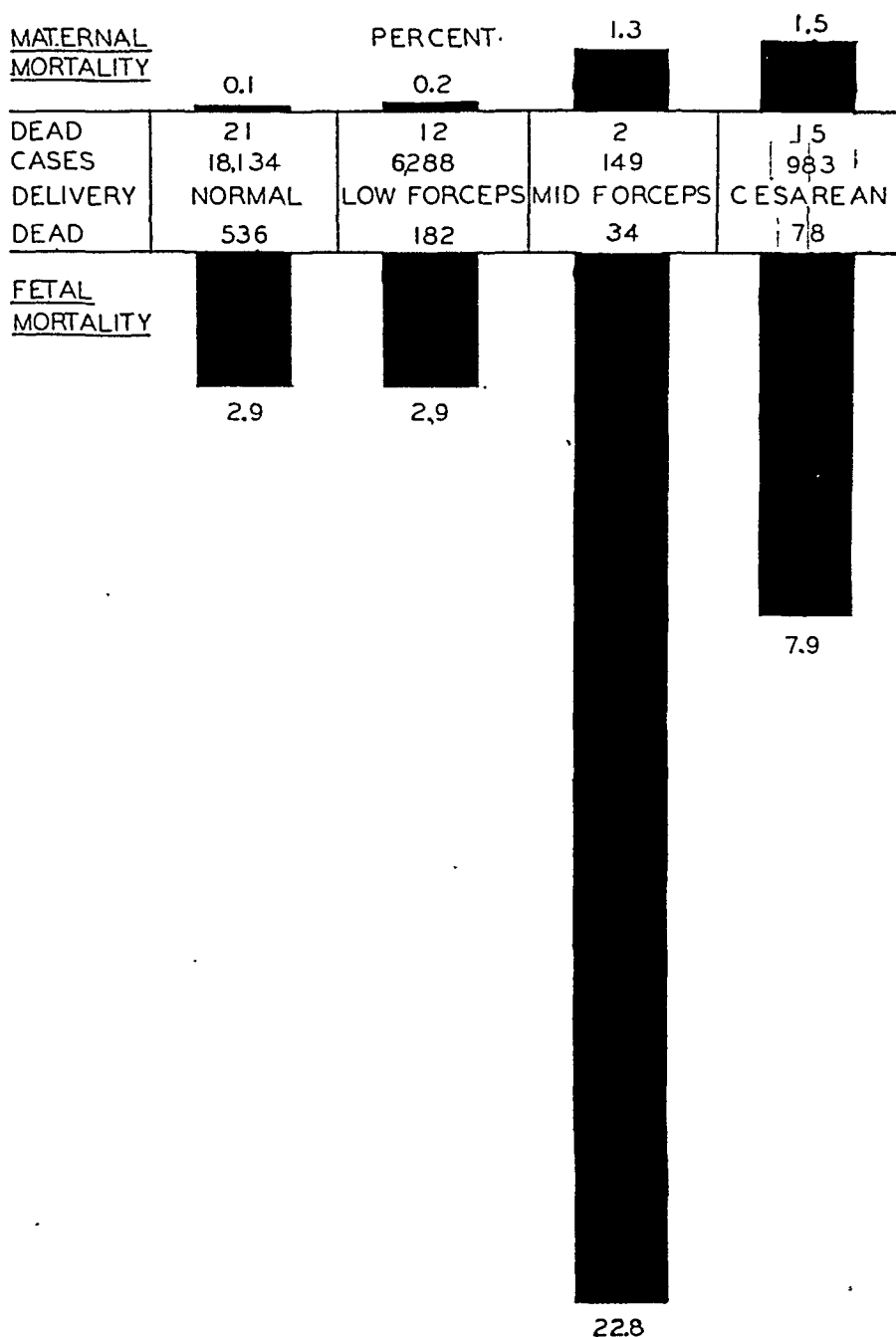


Fig. 1.

Incidence.—Fig. 2 shows the relative frequency with which cesarean section was employed during the ten years under study. It was performed relatively more than twice as often on private patients as on public ward patients. When this ten-year interval was divided into two periods of five years, each embracing approximately the same number of cesareans—almost a thousand, it is evident that although the total frequency had not changed much the individual fre-

quency, was less during the last five years in both parts of the hospital. Comparative percentages from other sources show an incidence of 6.1 per cent for the Cleveland Maternity Hospital,¹ 5.5 per cent for the Chicago Lying-In Hospital,² 3.9 per cent for the Methodist Episcopal Hospital of Brooklyn,³ 3.3 per cent for the State of Massachusetts,⁴ and 2.5 per cent for the City of Philadelphia in 1941.⁵ The total incidence at the Boston Lying-In Hospital during the ten-year period was 4.2 per cent, or one cesarean in every 24 deliveries; but this frequency was due to the relatively large number of cesarean sections performed on private patients. For the ten-year period, this was 6.7 per cent, or one in every 14 deliveries, a frequency higher than was reported from any of the sources quoted. Practically all the private patients were under the care of their

INCIDENCE OF CESAREAN SECTION

1934-1943 (10 YEARS)									
0	10	20	30	40	50	60	70	80	90 100 P.C.
1:31	3.2	P.C. PUBLIC		33,688	DELIVERIES		1,094	CESAREANS	
1:24	4.2	TOTAL		45,216			1,887		
1:14	6.7	PRIVATE		11,528			793		

1934-1938 (5 YEARS)

1:29	3.5	PUBLIC		17,444			604		
1:23	4.3	TOTAL		21,264			912		
1:12	8.1	PRIVATE		3,820			308		

1939-1943 (5 YEARS)

1:33	3.0	PUBLIC		16,244			490		
1:24	4.1	TOTAL		23,952			975		
1:16	6.2	PRIVATE		7,708			485		

Fig. 2.

obstetricians throughout pregnancy, and few were referred to them as consultants because of obstetric abnormalities. On the other hand, a large number of the public ward patients were referred to the hospital from Boston and neighboring parts of New England because they suffered from complications. No patient is refused admission. In such a group one would expect a higher incidence of cesarean sections, but the reverse proved true. One cannot escape the suspicion, therefore, that a number of the private cases of cesarean section might have been delivered by simple pelvic means if the accoucheurs had possessed a higher degree of patience. On the other hand, an incidence of 3.2 per cent, or 1 in 31, for the public ward cases is well in line with the frequencies quoted for other hospitals and is almost exactly the same as that for the State

RELATIVE FREQUENCY OF DIFFERENT TYPES OF CESAREAN SECTION

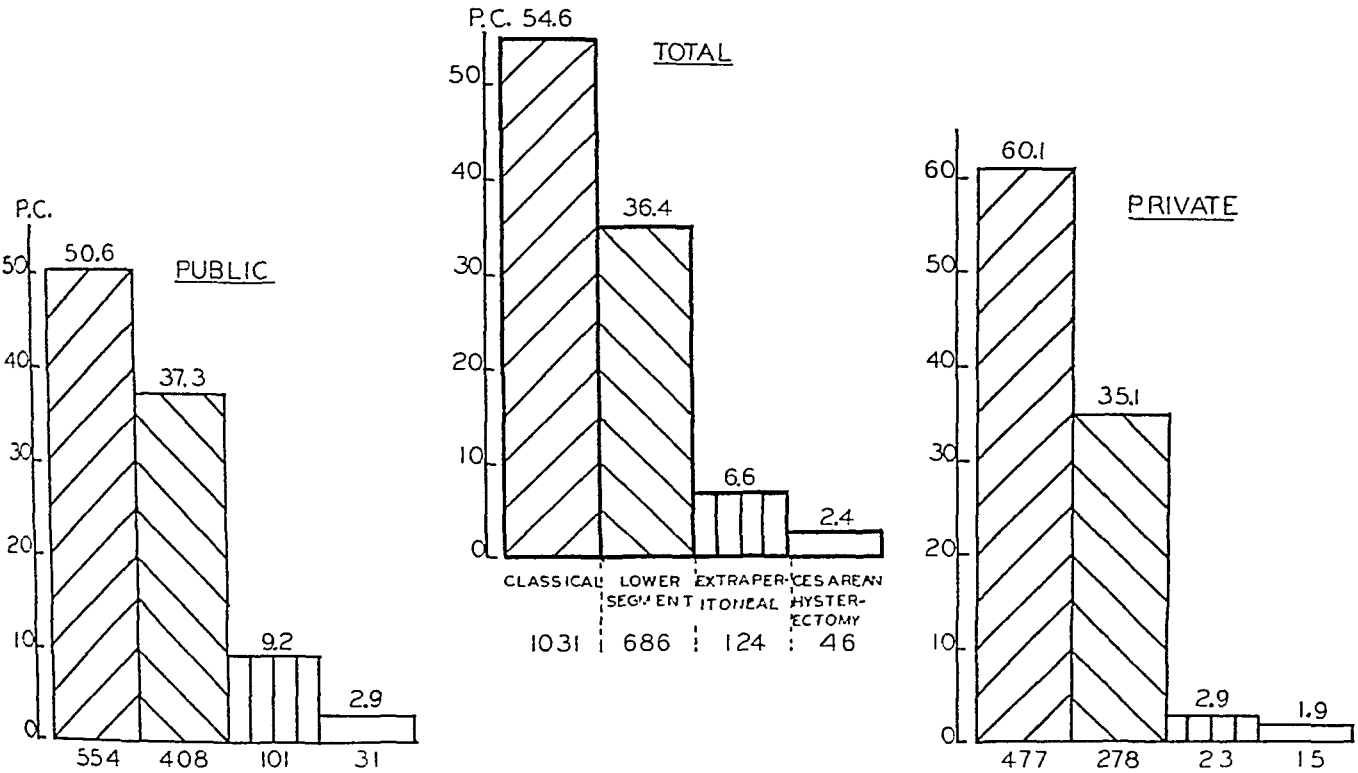


Fig. 3.

LOWER SEGMENT CESAREAN SECTIONS

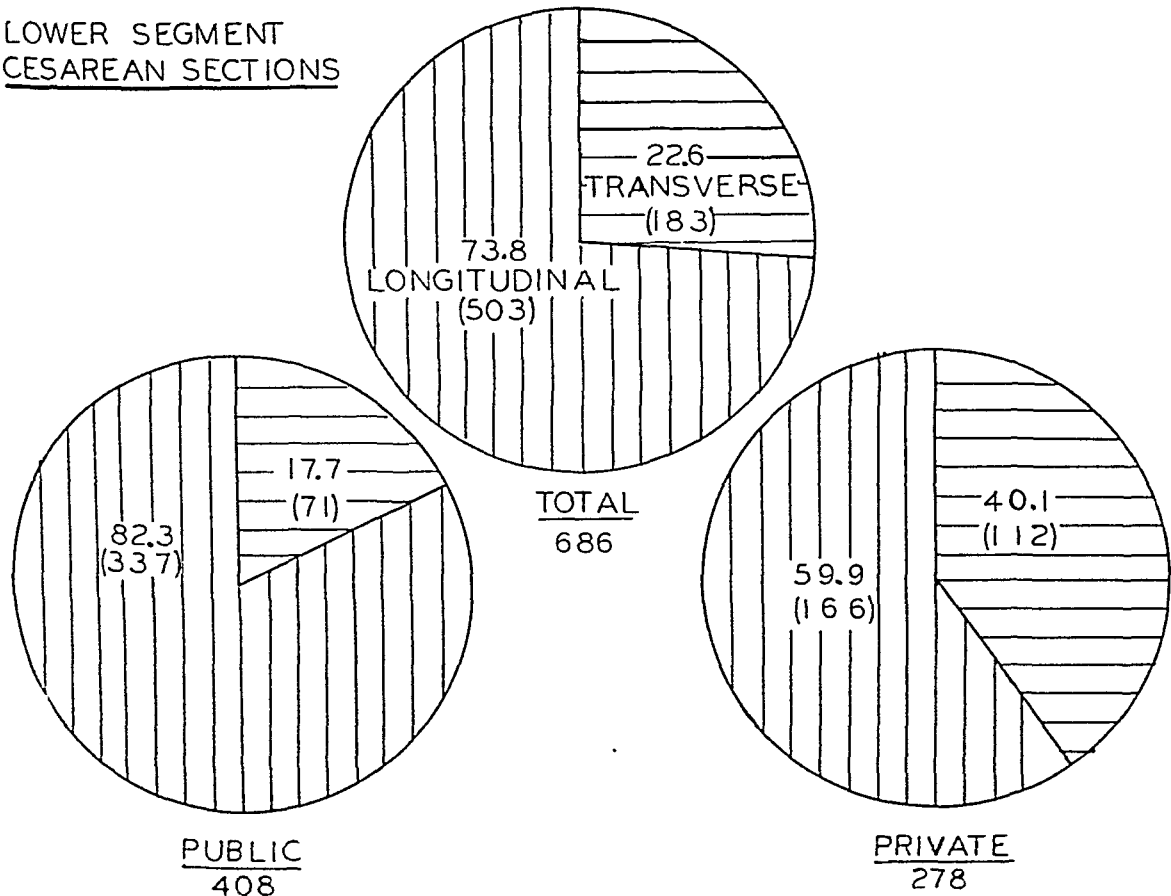


Fig. 4.

of Massachusetts. Fig. 1 also indicates that there were relatively fewer cesarean sections performed in both parts of the hospital during the last five years than in the first five years. The frequency among the private patients fell from 1 in 12 to 1 in 16, and among the public ward patients from 1 in 29 to 1 in 33, although the total incidence in the hospital remained approximately 4.2 per cent.

Fig. 3 shows that the classical cesarean section was performed in about half the public ward cases and in about three-fifths of the private cases. The lower segment operation was somewhat more popular on the public side of the hospital, but the chief differences were in the extraperitoneal type, which was increased three times, and in cesarean hysterectomy, which was one and one-half times more frequent. These differences reflected the greater number of complicated cases admitted to the public wards.

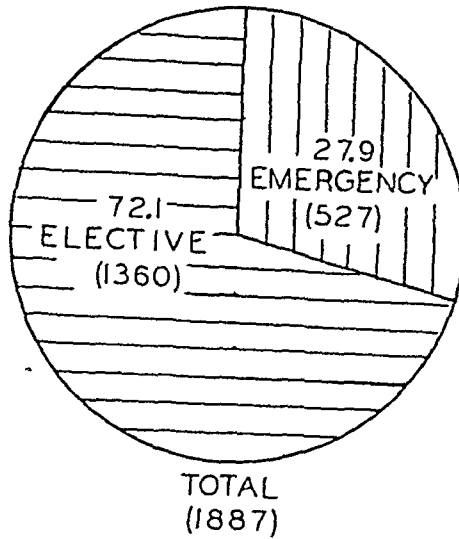


Fig. 5.

Fig. 4 demonstrates that the Kroenig (longitudinal incision) operation was performed in about three-fourths of all cases of lower segment operation, but that the preponderance was more marked on the public side than in the private wing, where two-fifths of the operations were of the transverse, or Kerr, variety.

TABLE I. RELATIVE FREQUENCY OF DIFFERENT TYPES OF EXTRAPERITONEAL CESAREAN SECTIONS

	ALL TYPES NO.	WATERS (NO.) (%)		LATZKO (NO.) (%)		SMITH EXCLUSION (NO.) (%)		MARSUPIALIZA- TION (NO.) (%)	
Public	101	40	39.6	38	37.6	14	13.9	9	8.9
Private	23	19	82.6	2	8.7	0	00.0	2	8.7
Total	124	59	47.7	40	32.1	14	11.3	11	8.9

Table I shows the relative frequency of the different types of extraperitoneal cesarean sections.

Fig. 5 indicates that about three-fourths of the operations were elective. This proportion holds for both the public and private patients.

TABLE II. FREQUENCY OF STERILIZATION

Total cesarean sections		1,887
Number sterilized		460
Per cent sterilized		24.4
Types of operations:	(No.)	(%)
Irving	414	90.0
Pomeroy	39	8.5
Salpingectomy	3*	9.7
Partial salpingectomy	2	0.4
Defundation of uterus	2	0.4
	460	100.0

*One following an unsuccessful Pomeroy in the last pregnancy.

Table II shows that approximately one-fourth of all cases (24.4 per cent), both public ward and private, were sterilized at the time of operation. Comparable figures are those of 33.7 per cent for the City of Philadelphia in 1941, and 46.5 per cent for the Chicago Lying-in Hospital. Two patients who had been subjected to the Pomeroy method of sterilization had become pregnant.

OPERATORS. NUMBER OF INDIVIDUAL OPERATORS: 177

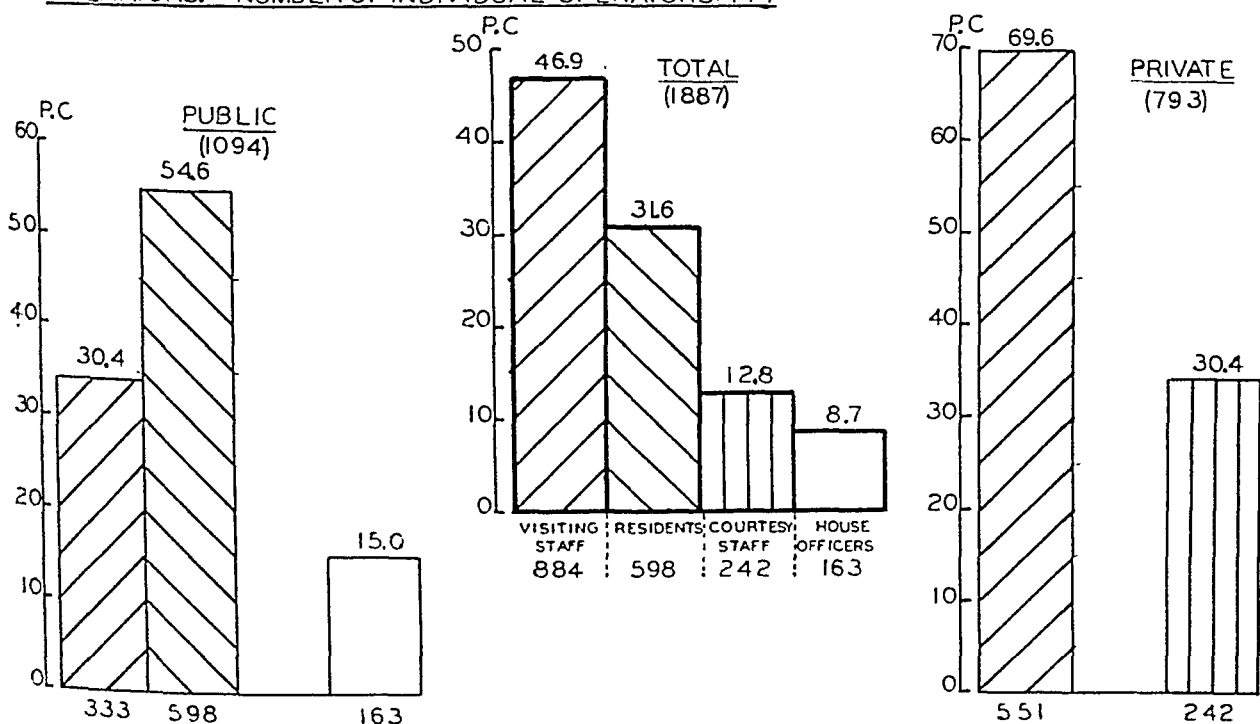


Fig. 6.

On the other hand, 413 patients, or 90 per cent of those sterilized, were operated on by Irving's method, which, in brief, consists of division of the tubes about $1\frac{1}{2}$ inches from their uterine ends and their implantation into the myometrium, where they are stitched in place. No failures have resulted from this operation. Although the Pomeroy or Madlener operation is easy, it is unsuccessful often enough so that the operator may afford to spend a few more minutes performing an operation which offers the assurance of permanent sterility.

TABLE III. RELATIVE FREQUENCY OF VARIOUS TYPES OF ANESTHESIA

ANESTHETIC	PUBLIC		PRIVATE		TOTAL	
	(NO.)	(%)	(NO.)	(%)	(NO.)	(%)
N ₂ O-O ₂ -Ether	503	46.0	445	56.1	948	50.2
Spinal	71	6.5	190	24.0	261	13.8
Open ether	133	12.2	62	7.8	195	10.4
Local	145	13.2	25	3.2	170	9.0
Cyclopropane	103	9.4	38	4.8	141	7.5
Ether-O ₂	62	5.7	15	1.9	77	4.1
Vinethene	62	5.7	1	0.1	63	3.3
Pentothal	14	1.2	11	1.3	25	1.3
Avertin	1	0.1	6	0.8	7	0.4
Total	1,094	100.0	793	100.0	1,887	100.0

Table III lists the anesthetics employed. Nitrous oxide, oxygen, and ether were used in half the cases in the whole hospital. Spinal anesthesia, employed in 13.8 per cent, was the next most popular, but it was given over three and one-half times more often on the private than on the public side. A practical objection to spinal anesthesia in obstetrics is the frequency of postanesthetic headaches.

Fig. 6 shows that the resident obstetricians performed over half the operations on the public ward patients, and that in the entire hospital the visiting staff performed less than half. There were 177 different operators, and the largest number of cesarean sections performed by a single operator was 162.

Indications.—The cesarean sections may be divided into those performed before viability (151) which were done mostly for medical reasons, as dystocia was not a problem, and those after viability (1,736). Fourteen (9.3 per cent) of the operations before viability were for hemorrhage. Because the medical

TABLE IV. INDICATIONS FOR CESAREAN SECTION BEFORE VIABILITY (ABDOMINAL THERAPEUTIC ABORTION). TOTAL, 151 CASES

INDICATION	NUMBER
Rheumatic heart disease (Public 42, private 4)	46
Hypertension (Public 22, private 2)	24
Hemorrhage	14
Placenta previa	5
Premature separation placenta	6
Rupture of uterus	1
Threatened rupture of uterus	2
Pre-eclampsia	11
Chronic nephritis	9
Pulmonary tuberculosis	8
Previous erythroblastotic infants	7
Pyelitis or pyelonephritis	6
Multiple sclerosis	4
Puerperal psychosis	3
Epilepsy	3
Separation symphysis pubis, progressive muscular dystrophy, and repeated fetal abnormalities: 2 each	
Rheumatoid arthritis, otosclerosis, renal tuberculosis, bilateral nephrolithiasis, surgical absence of one kidney, phlebitis, salivation, Huntington's chorea, Hodgkin's disease, and chronic invalidism: 1 each	

All these patients were sterilized except 12 (7.9 per cent) who were operated on for the following reasons: pre-eclampsia 5, premature separation of the placenta 4, and placenta previa 3.

conditions which led to these therapeutic abortions were such that future pregnancies were contraindicated, all but 7.9 per cent were also sterilized. Those not sterilized were operated on for temporary reasons, such as pre-eclampsia and hemorrhage. The preponderance of operations on the public side for rheumatic heart disease and hypertension should be noted. (Table IV.)

CHIEF INDICATIONS AFTER VIABILITY

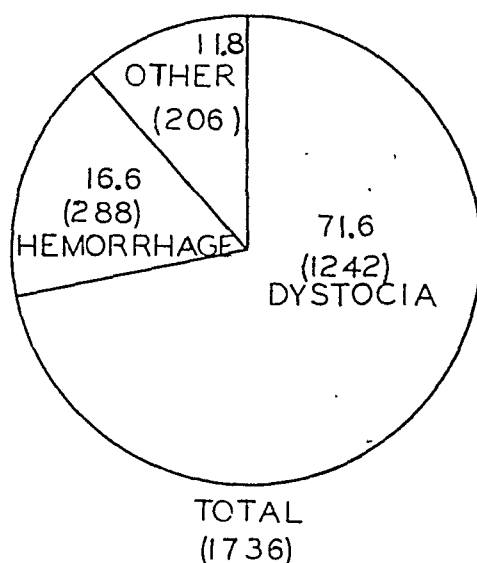


Fig. 7.

Fig. 7 shows the chief indications after viability. Seven-tenths of these operations were performed for dystocia; the rest for hemorrhage and miscellaneous reasons. These ratios compare closely for both the public and the private side.

TABLE V. DYSTOCIA AS AN INDICATION FOR CESAREAN SECTION AFTER VIABILITY (28 WEEKS); 1,242 OF 1,736 VIABLE PREGNANCIES

INDICATION	NUMBER
Previous cesarean section (Public 151, private 210)	361
Cephalopelvic disproportion (Public 181, private 75)	256
Contracted pelvis (Public 182, private 57)	239
Uterine inertia	178
Fetal distress	36
Breech	29
Gynecological repairs	27
Prolapsed cord	21
Fibroids	20
Elderly primiparity	18
Transverse	13
Previous myomectomies	7
Contraction ring	6
Previous stillbirths	6
Brow	5
Bicornuate uterus, face, and compound: 3 each	
Congenital absence cervix: 2	
Double cervix, urethral diverticulum, vaginal constriction ring, ankylosis of hip, prolapse of arm, elephantiasis, fractured pelvis, and sarcoma of sacrum and ilium: 1 each	

Table V deals with dystocia as an indication. A disproportionately large number of patients—210, or over one-fourth of the private cases—were operated on because they had had previous cesarean sections; but only 151, or about one-eighth of the public ward cases, were operated on for the same reason. It appears that a pelvic delivery after a cesarean section was a rarity on the private side. On the public side the requisites for a pelvic delivery under such circumstances are: the operation must have been done for a temporary indication such as placenta previa or a malpresentation, the convalescence must have been afebrile, the operation must have been performed by a competent surgeon, and the uterus must be explored after delivery for possible rupture. Between 1930 and 1941, 78 women with previous cesarean sections were delivered 118 times through the pelvis on the public side of the hospital without rupture of the scar occurring in a single case. Repeated cesarean sections were the chief indications for cesarean section in the entire hospital, comprising about one-fifth of all cases. Restriction of this indication would accomplish more than anything else to reduce the number of cesarean sections, particularly on the private side. Assuming that the 151 cesareans for this indication on the public side represent a reasonable figure, a comparable number for the private side would have been 109, or about half as many as were performed. As might be expected there were relatively more operations for cephalopelvic disproportion and contracted pelvis on the public side.

TABLE VI. HEMORRHAGE AS AN INDICATION FOR CESAREAN SECTION AFTER VIABILITY (28 WEEKS); 288 OF 1,736 VIABLE PREGNANCIES

INDICATION	NUMBER
Placenta previa	202
Premature separation of placenta	75
Rupture of uterus	10
Placenta accreta	1

Table VI, representing hemorrhage as an indication, suggests that the majority of the cases of placenta previa were delivered by cesarean section. On the other hand, most cases of premature separation of the placenta, particularly the type with internal hemorrhage—*ablatio placentae*—were delivered through the pelvis.

TABLE VII. OTHER INDICATIONS FOR CESAREAN SECTION AFTER VIABILITY (28 WEEKS); 206 OF 1,736 VIABLE PREGNANCIES

INDICATION	NUMBER
Pre-eclampsia (Public 71, private 59)	130
Rheumatic heart disease (Public 28, private 7)	35
Hypertension	17
Dermoid cyst, separation of symphysis, and for sterilization:	3 each
Eclampsia, osteitis fibrosa cystica, chronic nephritis, and no indication given:	2 each
Pyelitis, congenital heart disease, multiple myelomas, acute appendicitis, previous sterility, previous postpartum hemorrhage, and postmaturity:	1 each

Only 130 cesarean sections were performed for pre-eclampsia and these cases were proportionately divided between the two sides of the hospital. (Table VII.) There is a considerable preponderance of rheumatic heart disease on the public side of the hospital because many of these patients are referred by outside doctors. Only three patients were subjected to cesarean section so that they might be sterilized—all on the private side. The policy governing the public ward patients is opposed to cesarean section for this purpose, nor is it the custom of the hospital to perform sterilizations through a keyhole incision within the first twenty-four or forty-eight hours after pelvic delivery. (Table VIII.)

TABLE VIII. INDICATIONS FOR STERILIZATION WITH VIABLE PREGNANCIES (ENTIRE HOSPITAL); 321 OF 1,736 CASES (18.5 PER CENT)

	NUMBER	PER CENT
Previous cesareans	213	66.4
Gynecologic operations	29	9.4
Hypertension	25	7.8
Rheumatic heart disease	24	7.5
Excessive multiparity	17	
Fibroids	3	
Pulmonary tuberculosis	2	
Multiple sclerosis, osteitis fibrosa cystica, multiple myelomas, myesthesia gravis, chronic nephritis, surgical absence one kidney, previous post-partum hemorrhage, separation symphysis pubis: 1 each		

TABLE IX. INDICATIONS FOR CESAREAN HYSTERECTOMY

INDICATION	PUBLIC	PRIVATE	TOTAL
Rupture of uterus	10	2	12
Postpartum hemorrhage	1	7	8
Intrapartum infection, actual or suspected	7	0	7
Placenta accreta	6	1	7
Fibroids	4	3	7
Sterilization	3*	2	5
Total	31	15	46

*One for a previous Pomeroy sterilization that was unsuccessful.

Table IX shows, as might be expected, that rupture of the uterus was more common on the public side. Postpartum hemorrhage following cesarean section sufficiently severe to necessitate removal of the uterus was seven times more common on the private side. This discrepancy is difficult to explain unless it be that hemorrhages were more effectively treated on the public than on the private side. On the other hand, hysterectomy for infection was more common on the public side.

Special Diagnostic or Therapeutic Measures.—X-rays were taken on two-thirds of the cases on the public side and twice as often as on the private side (Fig. 8). They were employed more often for pelvic measurements in dystocia cases on the public side, as well as for general diagnostic purposes, but less often for the detection of possible placenta previa.

Since multiple pregnancy usually appears once in 87 cases, it occurred less often than usual (1 in 122) on the public side, and more often than usual

(1 in 54) on the private side (Table X). X-rays were taken in 31.2 per cent of the cases of multiple pregnancy on the private side and 24.4 per cent on the public side. When twins or triplets are suspected, a confirmatory x-ray is practically the rule; hence it would appear that in over half the cases on both sides of the hospital, the operator may have been surprised when he delivered twins at cesarean section.

TABLE X. MULTIPLE PREGNANCY

	INFANTS (NO.)	TWINS (PAIRS) (NO.) (RATIO)	TRIPLETS (SETS) (NO.) (RATIO)	MULTIPLE PREGNANCY (NO.) (RATIO)
		9 1:122	0 0:0	9 1:122
Public	1,103	15 1:54	1 1:810	17 1:48
Private	810	—	—	—
Total	1,913	24 1:80	1 1:1,913	26 1:74

TABLE XI. TRANSFUSIONS

	NO. OF CESAREANS	PATIENTS TRANSFUSED	PER CENT
Public	1,094	95	8.7
Private	793	20	2.5
Total	1,887	115	6.1

Transfusions were performed three times more often on the public side (Table XI). In the whole hospital, patients undergoing cesarean section were transfused at the rate of one in every 16. A relatively small number of patients required uterine packing (Table XII).

TABLE XII. UTERINE TAMPONADE

	NO. OF CESAREANS	NUMBER PACKED	PER CENT
Public	1,094	19	1.7
Private	793	12	1.5
Total	1,887	31	1.6

TABLE XIII. ADDITIONAL OPERATIONS; 35 OF 1,887 CASES (1.9 PER CENT)

OPERATION	NUMBER
Myomectomy	21
Repair of incisional hernia	4
Oophorectomy	4
Appendectomy	3

Unilateral salpingo-oophorectomy, ventral suspension, and excision of adenomyoma: 1 each

Additional operations (Table XIII) were performed in about 2 per cent of the cases. The three appendectomies were performed on private cases.

Morbidity.—In determining morbidity the so-called international standard was used: any convalescence which showed a rise in temperature of 100.4° F. or more on any two successive days after the first day and before the eleventh, was considered febrile. Fig. 9 indicates that there was no appreciable difference in morbidity between the classical and lower segment operations, that the inci-

X RAYS

INDICATIONS

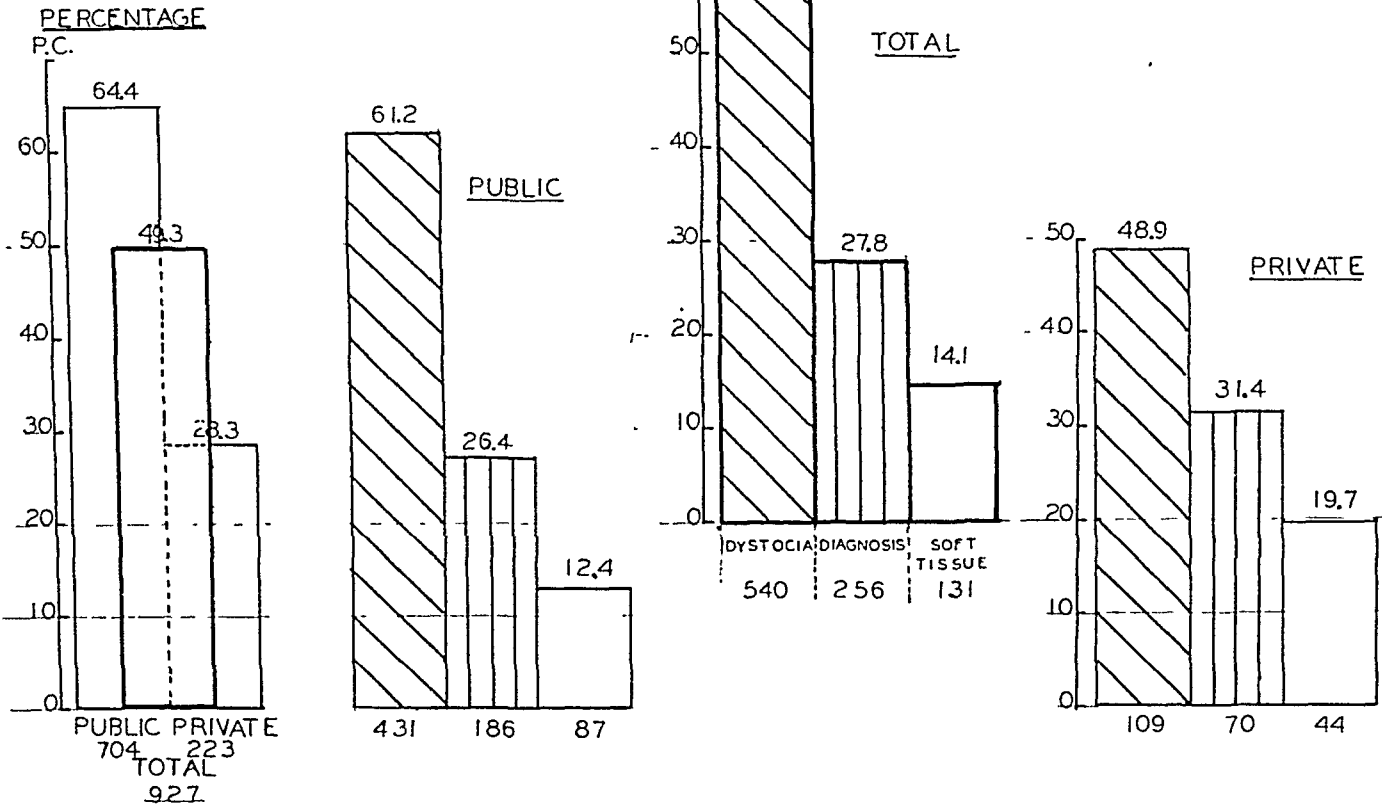


Fig. 8.

MATERNAL MORBIDITY IN DIFFERENT TYPES OF CESAREAN SECTION

P.C.

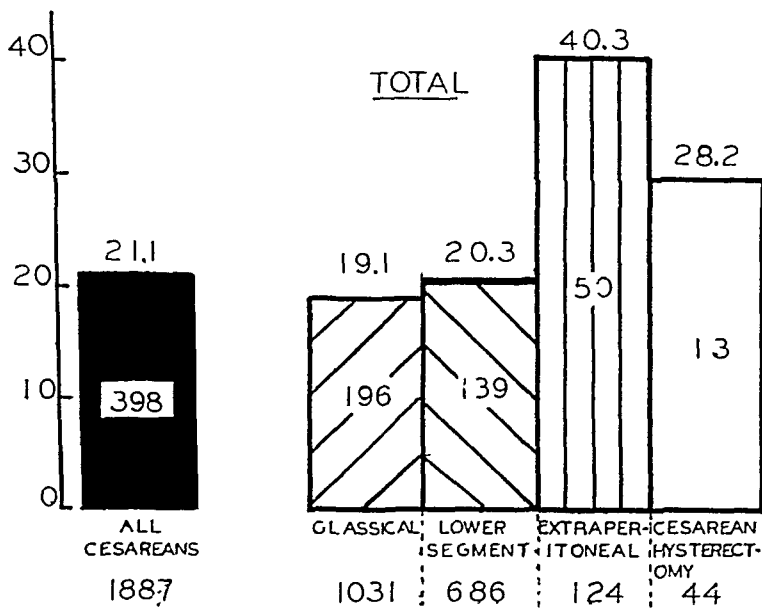


Fig. 9.

dence of morbidity was higher in cesarean hysterectomy, but that it was about twice as high in the extraperitoneal operation as in the classical and lower segment operations. Morbidity was notably lower in the private cases: 16.5 per cent in the private and 24.5 per cent in the public cases. The total morbidity was 21.1 per cent as compared with the usual hospital morbidity, which runs between $3\frac{1}{2}$ and 5 per cent. The Chicago Lying-in Hospital reports a morbidity of 43.8 per cent, the Cleveland Maternity Hospital 45 per cent, the Methodist Episcopal Hospital 50.1 per cent, and the City of New Orleans⁶ 61.3 per cent. The Boston Lying-In Hospital morbidity compares very favorably with all these; in fact, it is difficult to understand why they are so high. It has never been the policy at the Boston Lying-In Hospital to carry out any kind of vaginal antisepsis before cesarean section, and the relatively low morbidity following these 1,887 operations justifies this policy. Rupture of the abdominal wound following cesarean section occurred once in 629 cases and more often on the public side (Table XIV). There are no figures from other clinics available for comparison. The skin preparation for cesarean section was the same throughout the ten years. It consists of a soap and water scrub and the application of alcohol, ether, and $3\frac{1}{2}$ per cent tincture of iodine. Abdominal wounds are closed in layers with chromic catgut and the skin with silk. Stay sutures are seldom used.

TABLE XIV. RUPTURE OF ABDOMINAL WOUNDS

	NO. OF CESAREANS	NO. OF RUPTURES	RATIO
Public	1,094	2	1:547
Private	793	1	1:793
Total	1,887	3	1:629

TABLE XV. FETAL MORTALITY

	PUBLIC	PRIVATE	TOTAL
Total infants born	1,103*	810†	1,913
Nonviable infants	112	42	154
Viable infants	991 (89.8%)	768 (94.8%)	1,759 (91.9%)
Stillbirths of viable infants	28	11	39
Per cent: Stillbirths	2.8	1.4	2.2
Neonatal deaths of viable infants	50	31	81
Per cent: Neonatal deaths	5.0	4.0	4.6
Stillbirths and neonatal deaths	78	42	120
Net fetal mortality	7.8%	5.5%	6.8%
Total infants dead	190	84	274
Gross fetal mortality (nonviable, stillbirths, neonatal deaths)	19.0%	10.9%	15.6%

*1,094 single births plus 9 pairs of twins.

†793 single births plus 15 pairs of twins and 1 set of triplets.

Fetal Mortality.—There is lack of uniformity in reporting fetal mortality following cesarean section. Some authors record the gross fetal mortality, which consists of nonviable infants, stillbirths, and neonatal deaths; others report only stillbirths. It seems fair to eliminate nonviable infants, inasmuch as there was no expectation of obtaining a living child in these operations, which were in effect therapeutic abortions. It seems equally fair to count stillbirths and neonatal deaths occurring after the date of viability as fetal losses.

Table XV indicates that the total net fetal mortality was 6.8 per cent, that it was 7.8 per cent among the public ward cases and 5.5 per cent among the private cases. In comparing the fetal mortality of the Boston Lying-In Hospital in cesarean section with that reported from the sources already quoted, it appears to be about average (Table XVI). Table XVII indicates that there were an unduly large number of stillbirths on the public side, due to intrauterine asphyxia.

TABLE XVI. FETAL MORTALITY IN CESAREAN SECTION AS REPORTED BY VARIOUS AUTHORS; SERIES OF APPROXIMATELY 1,000 OR MORE CASES

AUTHORS	SOURCES	CESAREANS (NO.)	FETAL MORTALITY (%)
Manahan, Connally, and Eastman ⁷	John Hopkins Hospital	1,333	6.0
Daily ²	Chicago Lying-in Hospital	1,000	6.7
Mathews and Acken ³	Methodist-Episcopal Hospital	1,066	5.2
DeNormandie ⁴	State of Massachusetts	11,030	8.2
Kings ⁶	City of New Orleans	1,108	10.8

TABLE XVII. CAUSES OF STILLBIRTHS AND NEONATAL DEATHS

	NUMBER
Stillbirths:	39
Intrauterine asphyxia (Public 22, private 7)	29
Erythroblastosis	5
Hydrocephalus, intracranial hemorrhage, diaphragmatic hernia, broncho-pneumonia, and toxemia: 1 each	
Neonatal deaths:	81
Prematurity (Public 21, private 12)	33
Atelectasis (Public 12, private 9)	21
Intracranial hemorrhage (Public 8, private 4)	12
Pneumonia, erythroblastosis, and congenital heart disease: 4 each	
Atresia of esophagus, multiple congenital abnormalities, and congenital intestinal obstruction: 1 each	

TABLE XVIII. FETAL MORTALITY AMONG FULL-TERM INFANTS (OVER 5 POUNDS) WITH DIFFERENT ANESTHETICS USED IN CESAREAN SECTION; TOTAL CASES

ANESTHETIC	INFANTS (NO.)	STILLBIRTHS		NEONATAL DEATHS		TOTAL FETAL MORTALITY	
		(NO.)	(%)	(NO.)	(%)	(NO.)	(%)
N ₂ O-O ₂ -Ether	855	22	2.6	23	2.8	45	5.4
Spinal	203	4	2.0	4	2.0	8	4.0
Open ether	172	3	1.7	2	1.2	5	2.9
Local	103	1	1.0	9	8.7	10	9.7
Cyclopropane	116	1	0.9	3	2.5	4	3.4
Ether-O ₂	67	3	4.5	1	1.5	4	6.0
Vinethene	60	1	1.7	1	1.7	2	3.4
Pentothal	20	0	0.0	1	5.0	1	5.0
Avertin	7	0	0.0	0	0.0	0	0.0
Totals	1,603	35	2.2	44	2.7	79	4.9

In an attempt to determine the influence of anesthesia, if any, upon fetal mortality, two tables were prepared. The first (Table XVIII) shows the results obtained under different forms of anesthesia among full-term infants. Provided

the operation began with a living fetus in utero, anesthesia may be assumed to have had some possible effect in causing stillbirths. Its effect upon neonatal deaths is by no means so close, since other factors—notably prematurity—may come into play. Of the anesthetics most widely used, cyclopropane, local anesthesia, and open ether gave the best results so far as full-term infants were concerned.

Table XIX was prepared to determine the effect of anesthetics, if any, upon premature infants, since it is admitted that such fetuses in utero are more susceptible to drugs given to the mother than are full-term infants. Here spinal and local anesthesia gave the best results.

TABLE XIX. FETAL MORTALITY AMONG PREMATURE INFANTS (UNDER 5 POUNDS) WITH DIFFERENT ANESTHETICS USED IN CESAREAN SECTION; TOTAL CASES

ANESTHETIC	INFANTS (NO.)	STILLBIRTHS		NEONATAL DEATHS		TOTAL FETAL MORTALITY	
		(NO.)	(%)	(NO.)	(%)	(NO.)	(%)
N ₂ O-O ₂ -Ether	54	3	5.5	20	37.1	23	39.0
Spinal	38	1	2.6	7	18.4	8	21.0
Local	35	1	2.8	11	31.4	12	34.2
Cyclopropane	13	0	0.0	4	30.8	4	30.8
Open ether	6	0	0.0	1	16.7	1	16.7
Ether-O ₂	5	0	0.0	0	00.0	0	00.0
Vinethene	2	0	0.0	1	50.0	1	50.0
Pentothal	2	0	0.0	1	50.0	1	50.0
Totals	155	5	3.2	45	29.0	50	32.2

TABLE XX. MATERNAL MORTALITY, 1934 TO 1943 INCLUSIVE

	NO. OF CESAREANS	DEATHS	PER CENT
Public	1,094	15	1.4
Private	793	9	1.1
Total	1,887	24	1.3

TABLE XXI. MATERNAL MORTALITY IN THE TWO FIVE-YEAR PERIODS BETWEEN JAN. 1, 1934, AND JAN. 1, 1944

PERIODS	NO. OF CESAREANS	DEATHS	PER CENT
First 5-year period (1934-1938 inclusive)			
Public	604	12	2.0
Private	308	5	1.6
Total	912	17	1.9
Second 5-year period (1939-1943 inclusive)			
Public	490	3	0.6
Private	485	4	0.8
Total	975	7	0.7

Maternal Mortality.—The total maternal mortality for the ten-year period (Table XX) was 1.3 per cent. It was 1.1 per cent on the private side and 1.4 per cent on the public side. When we divide the ten years into two five-year periods, we find that the total mortality in the second period is approximately

one-third of that in the first, being 0.7 per cent (Table XXI). We also see that in the last five years the mortality on the public ward was less than that on the private side, although the maternal mortality among the private patients had diminished by one-half. The death rate on the public side, however, was only one-third of its former figure. Comparing the maternal mortality rates with those quoted from the sources already mentioned, we find that the only comparable death rate is that of the Chicago Lying-in Hospital, which covers approximately half the number of cases in our ten-year series but may be compared with approximately the same number of our cases in the last five years. In the ten-year period, 1931 to 1941, the Cleveland Maternity Hospital, in 1,317 cesarean sections, also had a death rate of only 1.7 per cent (Table XXII).

TABLE XXII. MATERNAL MORTALITY IN CESAREAN SECTION AS REPORTED BY VARIOUS AUTHORS; SERIES OF APPROXIMATELY 1,000 OR MORE CASES

AUTHORS	SOURCES	CESAREANS (NO.)	MATERNAL MORTALITY (%)
Manahan, Connally, and Eastman ⁷	Johns Hopkins Hospital	1,333	2.5
Daily ²	Chicago Lying-in Hospital	1,000	0.8
Mathews and Acken ³	Methodist-Episcopal Hospital	1,066	3.18
DeNormandie ⁴	State of Massachusetts	11,030	2.46
Kings ⁶	City of New Orleans	1,108	5.9
Lull ⁵	City of Philadelphia	894	2.46
Barney, Fish, and Riemen- schneider ¹	Cleveland Maternity	1,317	1.7

Fig. 10 shows the maternal mortality in various types of cesarean section. The general mortality was somewhat better with the classical operation than with the lower segment operation, and, as might be expected, there is an increased mortality with the extraperitoneal operation and with cesarean hysterectomy. It is noteworthy that 278 lower segment operations were performed on the private side with only one death, a mortality rate of 0.4 per cent. Morbidity and mortality was considerably lower in the elective than in the emergency operations (Table XXIII).

TABLE XXIII. MORBIDITY AND MATERNAL MORTALITY IN ELECTIVE AND EMERGENCY CESAREAN SECTIONS

	TOTAL	FEBRILE		DIED	
		(NO.)	(%)	(NO.)	(%)
Elective	1,360	252	18.5	14	1.0
Emergency	527	146	28.8	10	1.9

TABLE XXIV. MATERNAL MORTALITY IN DIFFERENT TYPES OF LOWER SEGMENT CESAREAN SECTION

	KROENIG (LONGITUDINAL INCISION)			KERR (TRANSVERSE INCISION)		
	(NO.)	(DEATHS)	(%)	(NO.)	(DEATHS)	(%)
Public	337	3	0.9	71	2	2.8
Private	166	1	0.6	112	0	0.0
Total	503	4	0.8	183	2	1.1

Table XXIV indicates that in the entire hospital a somewhat lower mortality was obtained with the Kroenig (longitudinal incision) operation than with the Kerr (transverse incision), although better results with the Kerr operation were obtained on the private than on the public side.

TABLE XXV. MATERNAL MORTALITY IN DIFFERENT TYPES OF EXTRAPERITONEAL CESAREAN SECTION

	WATERS			LATZKO			SMITH EXCLUSION			MARSUPIALIZATION		
	(NO.)	(DEATHS)	(%)	(NO.)	(DEATHS)	(%)	(NO.)	(DEATHS)	(%)	(NO.)	(DEATHS)	(%)
Public	40	2	5.0	38	1	2.6	14	0	0.0	9	0	0.0
Private	19	0	0.0	2	0	0.0	0	0	0.0	2	0	0.0
Total	59	2	3.4	40	1	2.5	14	0	0.0	11	0	0.0

Table XXV indicates that of the different types of extraperitoneal cesarean section the lowest mortality followed the Smith exclusion and the marsupialization operations. It should be realized, however, that these operations, particularly the Smith exclusion, were employed in cases where infection was not always definitely established.

TABLE XXVI. CAUSES OF DEATH

CAUSES OF DEATH	PUBLIC	PRIVATE	TOTAL
Peritonitis	7	3	10
Hemorrhage	2	5	7
Pulmonary embolism	2	1	3
Eclampsia	1	0	1
Intestinal obstruction	1	0	1
Bronchopneumonia	1	0	1
Malignant endocarditis	1	0	1
Total	15	9	24

Table XXXVI, listing the causes of death, indicates a preponderance of fatalities from peritonitis on the public side and from hemorrhage on the private side. There was only one death in the 1,887 cases which was attributed to anesthesia. This patient took her anesthetic badly, regurgitated vomitus, and died on the second postoperative day of bronchopneumonia. Of the ten cases that died from peritonitis, five had been in labor for periods of five, seventeen, seventeen, twenty, and twenty-six hours, respectively; the membranes had been ruptured in three cases for three, thirty, and ninety-six hours, respectively; and a fever was present in four cases. Two patients had respiratory infections; one of these women was operated on under local, and one under spinal anesthesia, but while pneumonia did not develop in either case, peritonitis did. One of these two patients was in labor and the operation was of an emergency nature; the other, however, was not in labor and the operation could have been postponed. These factors would indicate, since six of the operations were of the classical and four of the lower segment type, that greater safety might have been secured for these patients had the extraperitoneal approach been used, particularly since none of the three deaths following the 124 extraperitoneal cesarean sections resulted from infection. If the uterine contents is infected at

MATERNAL MORTALITY IN DIFFERENT TYPES OF CESAREAN SECTION

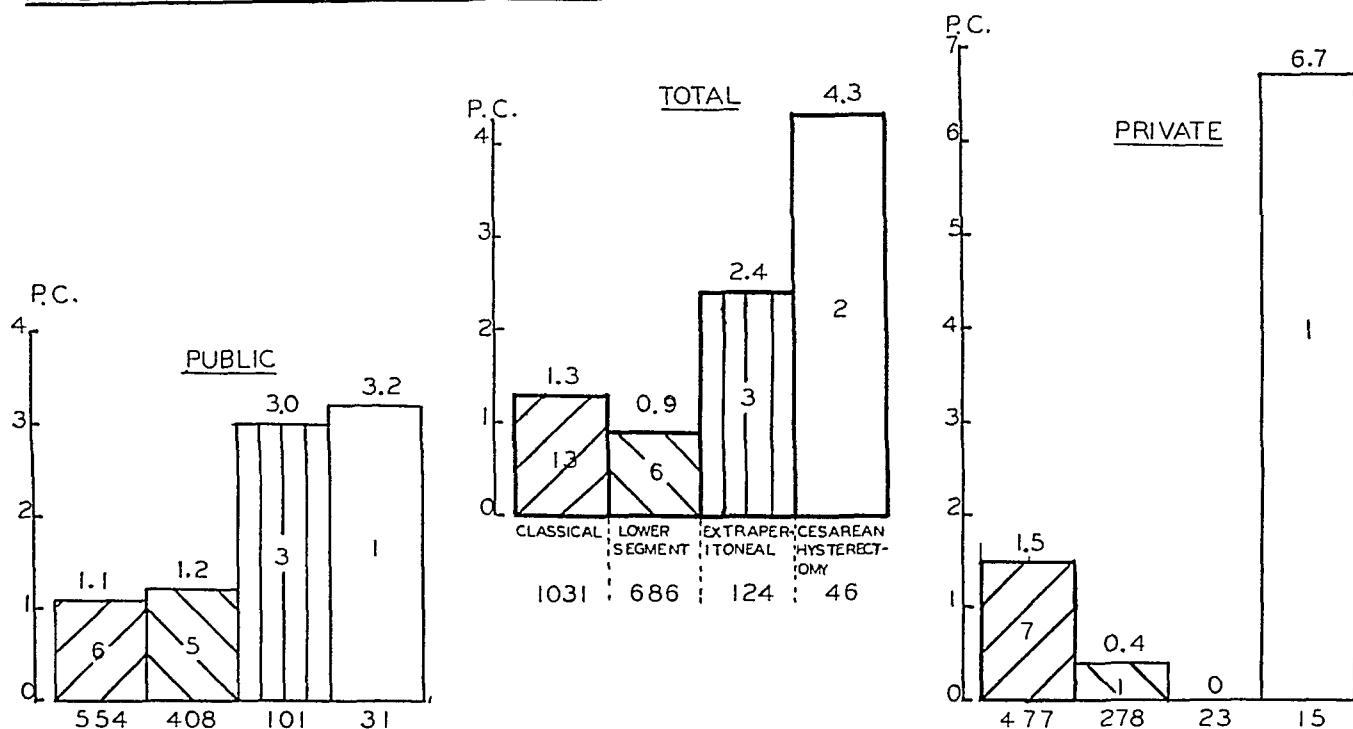


Fig. 10.

CLASSICAL AND LOWER SEGMENT CESAREANS COMPARED

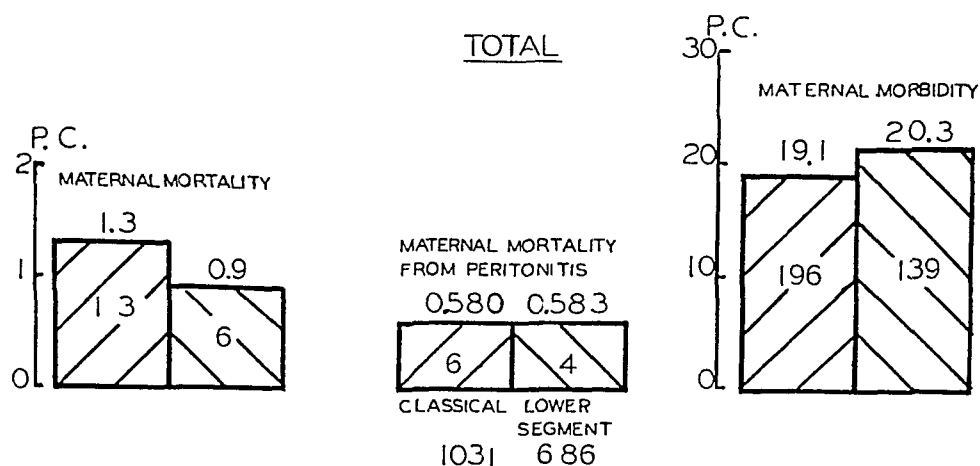


Fig. 11.

the time of operation we believe that the lower segment operation gives no greater security against peritonitis than does the classical.

Fig. 11 indicates that there was little difference in general maternal mortality, mortality due to peritonitis, and morbidity between the lower segment and the classical operation.

TABLE XXVII. MATERNAL MORTALITY ACCORDING TO STAFF POSITION OF OPERATORS

OPERATORS	NO. OF CESAREANS	NO. OF DEATHS	PER CENT
Visiting staff	884	12	1.4
Residents	598	7	1.2
Courtesy staff	242	4	1.6
House officers	163	1	0.6
Total	1,887	24	1.3

A glance at Table XXVII would suggest that the best way to secure a low death rate in cesarean section would be to delegate all the operating to the least experienced persons on the staff—the house officers, or interns. It should be obvious, however, that cases for operation, aside from the private patients, were assigned according to their seriousness. Moreover, the fact that 1,887 operations were performed by 177 operators with uniformly good results should indicate that why, when, and how the operation is done is quite as important as who does it.

The advocates of spinal anesthesia list as one of its advantages the alleged fact that the uterus contracts well at cesarean section. Table XXVIII, however, shows that it contracted so badly in three of 261 cases that it was necessary to remove it. Indeed, unless one accepts the relatively high incidence of hysterectomy for hemorrhage with ether-oxygen anesthesia in a small series of 77 cases, it does not appear that any anesthetic had a predominant effect toward producing postpartum hemorrhage in this series.

TABLE XXVIII. ANESTHESIA AND HYSTERECTOMY FOR HEMORRHAGE AT CESAREAN SECTION

ANESTHETIC	NO. OF CESAREANS	NO. OF HYSTERECTOMIES	PER CENT
N ₂ O-O ₂ -Ether	948	3	0.31
Spinal	261	3	1.14
Ether-oxygen	77	2	2.59

Cesarean Section as a Method of Delivery in Certain Complications of Pregnancy and Labor Other Than Dystocia.—Tables XXIX, XXX, and XXXI are designed to show the advantages or disadvantages of cesarean section compared with pelvic delivery in three of the common complications of pregnancy. These data are taken entirely from the public service. Table XXIX shows that cesarean section was the favorite method of treating placenta previa as it was employed in almost two-thirds of the cases. Among the patients so delivered, 113, there was only one death, a mortality rate of 0.9 per cent. The death rate was three times lower than the rate among those delivered through the pelvis; moreover, the fetal mortality was only one-fourth as high. In fairness, however,

TABLE XXIX. CESAREAN SECTION IN THE TREATMENT OF PLACENTA PREVIA. 181 PUBLIC WARD CASES. 1934 TO 1943

DELIVERED BY	NO. OF CASES	% OF TOTAL	MATERNAL DEATHS	MATERNAL MORTALITY %	STILLBIRTHS AND NEONATAL DEATHS	FETAL MORTALITY (%)
Cesarean	113	62.5	1	0.9	17	15.2
Other methods	68	37.5	2	2.9	41	60.4
Totals	181	100.0	3	1.6	58	32.0

TABLE XXX. CESAREAN SECTION IN THE TREATMENT OF PREMATURE SEPARATION OF THE PLACENTA; 368 PUBLIC WARD CASES, 1934 TO 1943

DELIVERED BY	NO. OF CASES	% OF TOTAL	MATERNAL DEATHS	MATERNAL MORTALITY %	STILLBIRTHS AND NEONATAL DEATHS	FETAL MORTALITY (%)
Cesarean	45	14.2	1	2.4	8	17.8
Other methods	323	85.8	7	2.2	140	43.3
Totals	368	100.0	8	2.2	148	40.3

TABLE XXXI. CESAREAN SECTION AS A METHOD OF DELIVERY IN PRE-ECLAMPSIA; 2,877 PUBLIC WARD CASES, 1934 TO 1943

DELIVERED BY	NO. OF CASES	% OF TOTAL	MATERNAL DEATHS	MATERNAL MORTALITY %	STILLBIRTHS AND NEONATAL DEATHS	FETAL MORTALITY (%)
Cesarean	76	2.7	1	1.3	12	15.7
Other methods	2,801	97.3	9	0.3	238	8.5
Totals	2,877	100.0	10	0.3	250	8.7

it must be stated that cases where the fetus was dead, nonviable, or grossly malformed were usually selected for pelvic delivery. Probably the indications for cesarean section in placenta previa can be extended. On the other hand, cesarean section was not the method of choice for delivering patients with premature separation of the placenta, as only slightly over one-eighth were delivered that way (Table XXX). It should be understood that all cases of premature separation of whatever degree of seriousness are included in this total, and that almost all cases of ablatio placentae were delivered through the pelvis as is suggested by the high fetal mortality (43.3 per cent). Cesarean section in premature separation was reserved for cases where the baby was alive, the degree of blood loss slight to moderate, and shock absent. The only exceptions were made when conservative measures—rupture of the membranes and the application of a pressure abdominal binder—were ineffective in bringing about delivery. There appears to be no reason to change this policy. It is evident from Table XXXI that conservative measures, either spontaneous or artificial, for evacuation of the uterus in pre-eclampsia was the rule, as only 2.7 per cent were delivered by cesarean section. This operation was reserved for cases where delivery was urgently indicated and the cervix, being long and rigid, was unfavorable for induction. The results confirm the wisdom of this policy. Pelvic delivery was accompanied by a maternal mortality of one-fourth and by a fetal death rate of about one-half of that in cesarean section.

We are now in a position to answer the questions raised in the first part of this paper: (1) Judging by the frequency of cesarean section in other institutions, the incidence among the public ward patients at the Boston Lying-In Hospital does not appear excessive. The relative frequency among the private patients on the other hand, being over twice that of the public ward, is the highest reported from any clinic, the only comparable figure being that from the Cleveland Maternity—6.3 per cent among its service cases. (2) The chief causes of maternal death on the public side was peritonitis and on the private side hemorrhage. Peritonitis might have been avoided by more frequent resort to extraperitoneal cesarean in questionable cases, and deaths from hemorrhage by more prompt transfusion. During the past year a hospital blood bank has been established where an adequate supply of group O, Rh-negative blood is always on hand. This precaution should do much to diminish the number of deaths from hemorrhage. The chief cause of stillbirth was intrauterine asphyxia, and the chief causes of neonatal death were prematurity, atelectasis, and intracranial hemorrhage. It should be remembered that a number of deliveries by cesarean section, particularly on the public side, were indicated in the interests of the mother, rather than those of the babies, and that in such cases a fairly high fetal death rate must be expected. In some cases, however, tests of labor, which were finally terminated by cesarean section, were extended to such a point that the fetuses suffered in utero and were either born dead or died in the early days of life. The twelve cases of intracranial hemorrhage belong to this group. (3) For the ten-year period the maternal mortality is somewhat lower on the private side, but for the last five years the maternal mortality is somewhat lower on the public side. Fetal mortality is distinctly lower on the private side and this is probably due to the fact that few, if any, long tests of labor were conducted, and fewer cesarean sections were performed there primarily for the sake of the mother. (4) Maternal mortality compares favorably with that reported from other clinics. The fetal mortality is about average.

References

1. Barney, W. R., Fish, J. S., and Riemenschneider, E. A.: *AM. J. OBST. & GYNEC.* 48: 733, 1944.
2. Daily, E. F.: *AM. J. OBST. & GYNEC.* 37: 348, 1939.
3. Mathews, H. B., and Acken, H. S., Jr.: *AM. J. OBST. & GYNEC.* 38: 956, 1939.
4. DeNormandie, R. L.: *New England J. Med.* 227: 533, 1942.
5. Lull, C. B.: *AM. J. OBST. & GYNEC.* 46: 314, 1943.
6. King, E. L.: *AM. J. OBST. & GYNEC.* 40: 860, 1940.
7. Manahan, C. P., Connally, H. F., Jr., and Eastman, N. J.: *AM. J. OBST. & GYNEC.* 44: 999, 1942.

A REVIEW OF THE PROBLEM OF CANCER OF THE CERVIX SINCE THE USE OF RADIUM IN 1912

BROOKE M. ANSPACH, M.D., PHILADELPHIA, PA.

*(From the Department of Gynecology and the Tumor Clinic of the Jefferson Medical
College Hospital)*

AT THE time this narrative begins, progress in the treatment of cancer of the cervix had been attempted mainly by improving the technique of the so-called advanced radical operation. This plan of operation had been preceded first by simple vaginal hysterectomy and then by high amputation of the cervix (Byrne) or vaginal hysterectomy (Werder) with the cautery.

W. A. Freund had followed by advising, in 1878, operation by the abdominal route, and a more radical procedure with dissection of the ureters had been suggested by Ries in 1895 and put into practice by Clark and Rumpf in 1896, the burden of the operator being the more extensive removal en bloc of the parts in contact with the carcinomatous cervix—the upper vagina, the parametrium, and the enlarged iliac and obturator pelvic glands.

The leaders in this and foreign countries vied with each other in the percentage of operability, mortality, and five-year results. It remained for Wertheim to publish first (1911) the operative results in a large series of patients (500); in half of them the operation had been performed more than five years previously. His percentage of operability was 50. His initial mortality was very high: 30 per cent of the first hundred, but reduced to 15 per cent in the last hundred and not at the expense of excluding the more advanced cases; 57.6 per cent of those surviving the operation and 42.9 per cent of all operative patients were alive and cancer-free at the end of five years; this meant an absolute survival rate of 18.4 per cent. The excellence of his work led to the adoption of the term "Wertheim operation" for the radical procedure.

In the days of which we have been speaking, when cancer affected the tissues to such an extent that no radical removal could be attempted, the carcinomatous areas were curetted and cauterized and the unfortunate victim was left to applications of acetone or formalin or to deodorizing douches for the foul discharge, and opiates for the pain.

The adoption of radium in 1912 as a treatment of choice by Kelly and Burnham, who by that time had approximately a gram of radium, marked the beginning of an epoch; the visual results of treating extensive cancers of the cervix were so startling as to seem miraculous. Here at last was an agent which had the power of destroying cancer cells.*

The gamma rays from a radium salt or a radium emanation and the gamma rays of the x-ray have loomed large as factors in the treatment of cancer ever since and, to a very considerable extent, have taken the place of radical surgery.

*Louis Wickham and his colleagues, particularly Cheron, should be credited with a limited number of cases prior to 1912; Kelly started in 1908 with a small amount of radium.

In the inevitable comparison between irradiation and operation there has been a constant effort by many writers to make a trustworthy estimate of the real worth of both forms of treatment. Many difficulties lie in the way, as will be shown, and in more recent years a combination of irradiation and operation have appeared to complicate the picture.

Extent of the Disease

To begin with, the extent of the lesion at the start of observation and treatment is of much importance. Schmitz first proposed (1927) a classification into four groups and this was modified later by others, among them the League of Nations Health Organization.

Cancer statistics have shown that the earlier the lesion is found the more effectual were all forms of treatment, and many efforts have been made to get hold of the cancer patient with the least delay. As early as 1905 the Section on Obstetrics, Gynecology and Abdominal Surgery of the American Medical Association had formulated a letter to be sent to every member of every County Medical Society emphasizing the early symptoms and recommending instruction of the lay woman.

Much good has been accomplished by the American Society for the Control of Cancer, now the American Cancer Society, which has publicized among women the early symptoms. This spread of information and the cancer clinics inaugurated by Catherine Macfarlane (1938) are bringing many patients, otherwise neglected, under a physician's care.

Physicians themselves have been warned against overlooking early symptoms and the Obstetrical Society of Philadelphia with the cooperation of the County Medical Society and the Department of Public Health has recently appointed a committee for the study of pelvic cancer. Every death from pelvic cancer in Philadelphia will be investigated and a special study made of that period of the patient's history between the onset of symptoms and the institution of adequate therapy—the so-called “delay period” and the responsibility for it assigned to the patient, the doctor, or the hospital, as the case may be. It may be noted here that the “delay period” nowadays is often due to a trial of hormone treatment before proceeding to a thorough diagnostic examination. The promiscuous use of hormones in women approaching the menopause is a real danger much to be regretted.

Diagnosis of Cancer

Biopsy of the cervix or diagnostic curettage with histologic examination remains the trustworthy diagnostic criterion; the color test of Schiller (failure of Lugol's solution to stain), the colposcope of Hinselman (magnified view of the vaginal and cervical mucosa), and the vaginal smear (cancer cell differentiation from benign epithelium) method of Papanicolaou and Traut, the last the more effective of the three, direct our attention to suspected patients.

Cullen's admirable book, *Cancer of the Uterus* (1900), was of the greatest help to the worker in the laboratory, and the magnificent histologic pictures by

Brödel and Becker, drawn cell for cell from beautifully cut and stained sections, gave an impetus to the differential histologic diagnosis. Notable also were the efforts in this direction of such men abroad as Ludwig Pick and Robert Meyer who instructed aspiring gynecologic pathologists from all over the world.

Technique of Irradiation

The individual patient must be very thoroughly studied as to the exact position and extent of the carcinomatous involvement; the irradiation must be effected just where it is needed with ample protection of the surrounding areas. For this purpose the screening of the radiant substances is of the greatest importance, and various forms of containers and screens have been devised.

The acme of radium applications is achieved only when a sufficient supply of radium salt or its emanation suitably screened is at hand at the moment of application. At the start of irradiation therapy the importance of screening was not appreciated everywhere and the necessary amount of radium or its emanation was to be found in a very limited number of hospitals.

As time went on, the situation improved, and this is very important because it frequently happens that the radiologist cannot be sure of what he will need until the parts are examined under anesthesia. The dose given will depend on the screening, the extent of the lesions, and the proximity of near-by structures that must be protected.

The dose for a cervical cancer is 3,600 mg. hr. and upwards, with 1.5 mm. of platinum screening; as much as 4,000 or 5,000 mg. hr. has been given. A "massive dose" at the first treatment has been the trend for a long while, since the cancer cells are supposed to be more vulnerable then than later when sclerosis and contraction of the surrounding tissues has taken place. Nevertheless some authorities (Heyman) believe in the smaller and repeated (fractional) applications and report excellent results.

The harmful rays, alpha and beta, are entirely excluded when the radium salt is enclosed in platinum capsules of 50 mg. contents with walls 1.5 mm. thick. An equivalent filter is 2.8 mm. of lead. For 10 mg. needles of the radium salt, a 0.5 mm. platinum wall is used which takes care of 99.9 per cent of the harmful rays and solid gold walls of 0.03 mm. thickness shuts out 97.6 per cent of the objectionable rays from emanation seeds.

The treatment of cancer of the cervix by x-ray began in Germany about 1911; it reached its greatest early development at the Erlangen Clinic under the direction of Seitz and Wentz. Deep x-ray therapy has acquired a position as a desirable preliminary or adjunct to nearly every application of radium. A question to settle is whether it should come before or after the application of radium. Theoretically no doubt it should be first, since the manipulation incident to a radium application might displace cancer cells and these may spell disaster unless they have been previously exposed to the deep x-ray.

We will not discuss at length the technique of the x-ray therapy used for cancer of the cervix since that lies without the province of the gynecologic radiologist. We content ourselves with saying that while x-ray machines of 200, 400, 800 kw. and over have been used, the standard treatment at the Jeffer-

son Hospital is given by a 200 kw. machine with suitable screening through four portals of entry both anteriorly and posteriorly, and an average exposure measured by erythema of 1,600 to 2,400 r. to each area. A transvaginal port exposure of the same dose has been added since 1944.

The histologic diagnosis must be settled before any form of irradiation is started; in the average patient with suspected cervical cancer this may be determined satisfactorily by a careful biopsy with a minimum disturbance of the parts, using a sharp knife or a scissors, and sealing the area with a cautery immediately thereafter; any more than the gentlest palpation of the uterus and surrounding parts should be avoided.

Among the radiologists we may presume that the work of Heyman has not been surpassed. One reason is that when he comes to make an application of radium, everything that may be required is at his disposal. In his clinic at Stockholm of a morning there are from 500 to 800 mg. of radium at hand and more available if needed, with every conceivable size and shape of platinum capsules, needles, and filters. Another reason is the government help in Sweden whereby all patients may be kept track of, the Government paying for their transportation to and from the Radium Hemmet, so that Heyman's statistics, reflecting his diligence and care, are extraordinary in the follow-up.

To be specific, he has not lost sight of a single one in a total of 2,387 patients, and he has reported upon them in extenso as to survival, deaths, and disappearances at least up to the beginning of World War II (1939) when his total of ten-year patients had reached 1,438.

Bonney has succeeded Wertheim as the outstanding exponent of radical surgery. It is interesting to note that Wertheim in 1911 had an absolute five-year salvage in 250 patients of 18.1 per cent, and that Bonney in 1941 reported his absolute five-year salvage in 500 operations as 25 or 26 per cent;* so much for improvement!

Technique of Operation

The advanced radical hysterectomy for cancer of the cervix is a formidable operation and few gynecologists learn to carry it out expertly. Those who undertake it must be skillful naturally, they must have abundant clinical material for their apprenticeship, they must be convinced that the high mortality and morbidity which almost inevitably will attend their first cases is justified by the better results that may be achieved and so go on with a preferment of the operation despite the immediate risk.

Apropos of this we may quote Shaw, a skillful and successful surgeon, who gave up the operation despite an experience comparing well with Bonney's, amounting to 154 five-year patients, in favor of irradiation; he speaks of "fearsome" operations, "the technical difficulties of which no description ever mentions"; and also Bonney who points out that "the safety and the outcome of the operation depends upon the judgment and skill of the surgeon which increases with his experience."

*Bonney gives two figures in all his reckonings; the first includes every patient; the second excludes the patients dead from other diseases or lost.

Not all operations labeled Wertheim are really so. There is no operation in the gynecologic field that requires more care in the selection and preparation of patients, better anesthesia, and more of the utmost in technique, judgment, and postoperative treatment.

So far as the further practice and development of the radical operation is concerned, it is doubtful whether other surgeons will go as far as the pioneers, Mackenrodt and Wertheim, especially, in Germany, and Berkeley and Bonney in England. We must remember that when they began their operative experience a surgical procedure was the only available means of curing a patient of cancer. They felt justified in taking any risk no matter how great because otherwise every patient was doomed to death.

After irradiation had appeared, the picture changed, for here was a remedy which, in a certain proportion of cases, gave as good results with almost no primary mortality and with a minimum of morbidity such as ureteral fistula and the distressing symptoms sometimes following an injury to the bladder or the rectum. It is all very well to say that the results of surgery will be greatly improved because of the modern methods of combating infection and of sustaining the operative patient, but the morbidity to a certain extent from injury will still remain. It will give many a surgeon pause to subject a patient to a formidable surgical procedure when he realizes that it may prove to be no better than irradiation.

Wertheim began his work in 1898; Bonney started in 1907; it was not until 1911 or 1912 that Kelly and Burnham had enough radium to start their work in earnest and the reports of the results of irradiation (five-year salvage) did not begin to appear until 1921 or 1922; by that time Bonney had had fifteen years of operative experience; he must have been satisfied with his work for he continued with it, turning over to the radiologist only the inoperable patients.

Results of Irradiation and Operation Combined

Whether a combination of surgery and irradiation as practiced by Lynch and Taussig, master surgeons, both unfortunately deceased, will accomplish more than the radium of a Heyman or the scalpel of a Bonney is a question for the future.

Lynch declared "that surgery should be reserved for the treatment only of patients whose cancers are limited definitely to the cervix and who themselves are first-class surgical risks by reason of age and general physical condition."

He used irradiation and an advanced radical operation in a selected group of patients and compares it with irradiation alone. He published charts illustrating the results at five and at ten years which favored definitely a combination of irradiation and operation.

In the five-year estimate the salvage rate of the combined procedures was 61.5 per cent; of irradiation, 53.1 per cent; in the ten-year estimate the salvage rate of the combination was 62.9 per cent; and of the irradiation, 36.7 per cent.

These are high degrees of accomplishment. The absence of recurrence in the irradiation plus operation group between the fifth and the tenth years shown

by Lynch in his charts may be very significant; Heyman and Bonney both had an increase in recurrence during the second five years of about 10 per cent; Lynch had approximately the same difference in the patients with irradiation alone, from 53.1 per cent at five years to 36.7 per cent at ten years, but in the irradiation plus operation group the rate of salvage is set down astonishingly as 61.5 per cent at the end of the first and 62.9 per cent at the end of the second five years.

Unfortunately we find no statement in his 1940 report as to the total number of patients or the other data that permits an appraisal of the absolute results.

Similarly Taussig in his 1943 report tells us that his lymphadenectomy patients were in Group II, younger and good operative risks from the standpoint of obesity and general condition. At that time he had had 175 patients of irradiation combined with lymphadenectomy and compared them to 118 patients for whom he had used irradiation alone; the five-year survival in the first group was 38.6 per cent; in the second 26.8 per cent. Taussig's data also are not given in such detail as to permit an estimate of his absolute percentage of results.

Removal of Carcinomatous Glands

Bonney in the last edition of his textbook reported the removal of glands that were malignant in 171 of his 415 operation patients between 1907 and 1931; 28 of them survived for ten years, 16 per cent, or, if those dying from intercurrent disease or lost are excluded, 18 per cent.

Taussig's removal of enlarged lymph glands was done in combination with irradiation because he doubted the curative effect of irradiation upon them; he did not remove the cervix or the surrounding tissue. In 175 patients subjected to the combined procedure, the glands were carcinomatous in 26.8 per cent; 21 per cent of the latter survived at the five-year salvage.

The ideas of Lynch and Taussig have been followed by D. G. Morton of the University of California. He selected for lymphadenectomy as Lynch did for hysterectomy only those patients in whom the local reaction to irradiation had been favorable. In a considerable experience with 65 patients, he found the glands carcinomatous in 15 but cancer-free in 28; the involvement of glands was four times more frequent in patients who had had no preoperative x-ray.

He raises a question that occurs to us also of whether it will be shown that modern x-radiation actually may destroy cancer in lymph nodes; if so there would be some doubt as to the need of lymphadenectomy.

We may contrast the reports of Heyman the radiologist and Bonney the surgeon as a matter of general interest. Heyman had a total of 1,438 ten-year patients and Bonney 451. Heyman's patients are definitely classified; Bonney does not classify his patients and the only way we have of judging them is by his operability rate (63) for the entire series, his operability rate in private patients (80) and the number of operations (171) in which he removed carcinomatous glands. We may infer from these facts that he had many early (Groups I and II) patients but also many late (Group III) ones, but we can go no further.

Heyman reports a ten-year salvage as follows: 44 per cent in Group I; 27 per cent in Group II; 11.7 per cent in Group III and 3.3 per cent in Group IV. His absolute rate of recovery for the entire series is 17.

Bonney reports an absolute ten-year salvage of 20 or 21 per cent of all cases and a relative salvage of 16 or 18 per cent in those (171) patients from whom he removed carcinomatous glands.

Practically all patients with carcinoma of the cervix may be treated with irradiation whereas operative treatment may be selected only for those in whom the disease has not advanced beyond certain limits; this at once has a large bearing on what are spoken of as absolute and relative results. The number in the entire group of consecutive patients coming under observation and treatment during a certain time, that are entirely free of signs or symptoms of the disease at the end of a standard period of years, constitutes the absolute percentage; the number in selected groups constitutes the relative percentage.

Another very important figure is the percentage of the total number of patients who are kept under observation up to the time of the report. Wertheim, in his paper of 1911, had not lost sight of a single patient. In our own clinic, when Scheffey came to make the first five-year estimate, the whereabouts of 30 to 40 per cent of the patients were unknown. By persistent efforts he was able to search out most of them, raising the follow-up to 94 per cent at the time of publication; since then, 98.6 per cent of our patients have been kept under observation. When patients are reported lost sight of or dead from other intercurrent diseases, an element of inaccuracy is injected into the summation of results. We may venture the opinion that at least two-thirds of them have died of cancer.

Although, at first, patients with no gross or symptomatic evidence of the disease at the end of five years were regarded as cured, it was soon observed that recurrences appeared later so that the term used was changed from "cured" to "salvaged." It has been shown finally that there are many recurrences between the fifth and the tenth year but rarely later, and whereas Heyman could report 22 per cent absolute salvage of all cases at the end of five years, the figure dropped to 17 per cent at the end of ten years; and Bonney's absolute salvage, 25 or 26 per cent at five years, fell to 20 or 21 per cent at ten years.

Some of the Fallacies of Cancer Statistics

The vagaries of cancer statistics have already been pointed out in the course of this paper. It is difficult to evaluate and to compare the results of treatment, whatever it has been, in different hands. The reports are not made uniformly and one must hesitate to draw conclusions of his own relative to the total number of patients, the classes to which they belonged, the five- and the ten-year salvage in absolute and in relative terms.

To obtain uniformity in records and in reports, "perhaps a goal we still shall gain," is most desirable, but the probabilities are against it. If such a thing began at once, a period of eleven years would have to elapse before ten-year salvage could be estimated. The comprehensive, exact, and discriminating reports of

George Gray Ward of the Woman's Hospital in New York took a lead early in the study of irradiation in this country and have steadily maintained it.

The difficulties attendant upon an estimate of the class to which a cancer patient belongs at the start have been mentioned, and the difficulties in determining from a personal examination or a written or verbal report at the end of ten years, which has become the standard salvage period, are quite obvious.

Another misinterpretation threatens when reirradiation is encountered. In Scheffey's report of 1943, 36 per cent of 285 five-year patients had been reirradiated; the result in them is hardly of the same import as in those who needed only one treatment; they really represent recurrences and should be dropped, perhaps, and their salvage period started all over again. The custom at present is to keep them in their original five- and ten-year units no matter when the recurrences.

The technique of all engaged in the treatment of cancer of the cervix may change from time to time, and up-to-date statistics for new procedures require six to eleven years.

In estimating results by combining reports from various sources, there is some fallacy because radiologic treatment and operative treatment are by no means of equal merit in different hands.

A bird's-eye view may lead to the conclusion that cancer statistics merely show "which way the wind is" and are capable of misinterpretation.

We take this occasion to acknowledge the work of such men as Healey, Keene, Crossen, Novak, Norman Miller, Behney, Te Linde, and Kamperman, who have not been spoken of previously, and others for the moment forgotten. Our criticisms have been with the best intention and a full realization of the trials of the investigator.

Prospects for the Future

There are numerous reasons to believe that irradiation may be applied better as time goes on and the radiotherapist is supplied with an adequate amount of the salt or the emanation, perhaps in a form that will be more effective no matter what the mechanical difficulties presented by the location of the cancer and the associated lesions in the particular case. A combination of irradiation with operation may be devised that will be more effective than either alone (Lynch, Taussig, Morton, Meigs).

It may be pertinent here to call attention to Bonney's results when every patient in his series is taken into account. As noted previously, he operated upon 63 in every hundred; 7 were beyond any form of treatment; 30 were irradiated and 1 in 5 or 6 recovered. On this basis he reaches an absolute five-year salvage of 30 or 31 per cent and a ten-year salvage of 24 or 25 per cent.

One cannot help believe that the riddle will be solved some time, with irradiation playing a large part, but maybe from some entirely new therapeutic means as yet unknown. In the last decade we have had reason to feel more hopeful of medical wonders to come. Gynecologists for years had looked for an intravenous treatment of septic infection; mercurochrome was the nearest approach to a medicine that might kill the infection and spare the patient, but

with that drug as with the others preceding it we had to acknowledge failure; yet finally the sulfonamides and the antibiotics (penicillin and streptomycin) were discovered, and a new and very advanced era began in the treatment of all forms of bacillary disease. Perhaps something revolutionary, a catalyst, that will specifically destroy cancer cells may be discovered.

In summing up, one may conclude that:

1. A greater number of cancer patients are presenting themselves in the early stage as a result of information given to the lay woman and to physicians in general; the proportion is almost bound to increase.

2. Irradiation with radium or its emanations, or by the deep x-ray, will become more widely and adequately available, better understood, and more effective.

3. The risk attending operative procedure has been much reduced and improvement is likely to continue. Of the 93 patients lost by Wertheim in his first 500 operations, the cause of death in 39 was put down as peritonitis. With the sulfonamides, penicillin, and streptomycin, with the use of glucose, plasma, and blood transfusion, with Wangensteen's drainage, with continuous spinal anesthesia, with prostigmine—a large proportion would have been prevented.

Meigs recently reports 47 cases of his Wertheim operation with preparatory radiation in 40 per cent and no immediate mortality; Lynch's (1940) figure was 73 radical operations with 4 deaths; Taussig (1936) 46 patients with 2 deaths. Bonney between 1907 and 1936 had performed his operation on 500 patients with 70 operative deaths, 14 per cent; in the last two hundred operations of the series the mortality had shrunk to 11 per cent. He points out the influence of the extent of the operation, as well as the age and general condition of the patient, on the primary mortality. Berkeley found in a collected series of operations by British gynecologists a mortality in advanced cases of 23.1 per cent; of early ones 6.3 per cent. Bonney estimates the risk in favorable cases as 5 and in unfavorable as 20.

4. Perhaps a combination of irradiation and operation will give better results.

During the period of time covered by this report there have been other means proposed that were believed to have a specific effect upon the cancer cell. The first of these was the theory of Beard (1905) that pancreatic ferments were curative. The second that of Blair Bell (1926) according to which lead would kill the cancer cell. Both of these plans have failed to meet the hopes held out for them and have been abandoned.

Percy's plan (1914) of cooking the carcinomatous areas by means of specially devised specula met with some early success but was lost in the advancing tide of irradiation.

We may quote with interest from an article that appeared recently in the *Statistical Bulletin* of the Metropolitan Life Insurance Company:

Among white females insured in the Metropolitan Life Insurance Company's Industrial Department, essentially an urban group, the standardized death rate from cancer at ages 1 to 74 declined steadily from 90.4 per 100,000 in 1934 to 80.3 in 1944, a decrease of 11 per cent.

There is confirmation from other sources as well that the organized movement to control cancer is bearing fruit. The educational campaign, which is a vital part of the whole program, is succeeding in having people, and more especially the women, seek diagnosis and

treatment earlier in the course of the disease, when the chances of cure are best. For example, among the patients at the cancer clinics in Massachusetts, the average delay between the first symptoms and visit to a physician was reduced from somewhat more than six months in the period, 1927 to 1935, to 3.3 months in 1943. If this accomplishment is not typical of the country as a whole, it at least has counterparts in many other clinical experiences.

The increasing control over cancer may also be attributed to a number of other factors. It is even likely that prevention has played some part. The close relation between cancer of the cervix of the uterus and neglected injuries at childbirth has been generally recognized. With the long-term fall in the birth rate and with marked improvements in obstetrical and postpartum care, the incidence of cancer of the female reproductive organs presumably has decreased. But far more important in the total picture, than prevention, has been the constantly increasing number of physicians trained to deal effectively with the disease, the marked increase in the public and private facilities for treatment, and the development of new and improved technique.

In conclusion I wish to acknowledge gratefully the help received from Dr. Lewis C. Scheffey in the preparation of statistical data used in this paper and for his criticism and advice.

References

- Berkeley, C., and Bonney, V.: *Textbook of Gynecological Surgery*, London, 1942, Cassell & Co., Ltd.
- Bonney, V.: *J. Obst. & Gynaec. Brit. Emp.* 48: 421, 1941.
- Burnham, C. F.: *Radio-therapy*, in Curtis, *Obstetrics and Gynecology*, Philadelphia, 1933, W. B. Saunders Company, p. 868.
- Idem: Personal communication, 1945.
- Healy, W. P., and Brown, R. L.: *AM. J. OBST. & GYNEC.* 38: 1, 1939.
- Heyman: *League of Nations Health Organization*, 1939.
- Kelly and Burnham: *J. A. M. A.* 45: 1874, 1915.
- Lynch, F. W.: *Tr. Am. Gynec. Soc.* 56: 229, 1931.
- Idem: *Treatment of Cancer and Allied Diseases*, by G. T. Pack and E. M. Livingston, editors, New York, 1940, Paul B. Hoeber, Inc.
- Meigs, J. V.: *Surg., Gynec. & Obst.* 38: 195, 1943.
- Miller, N. F.: *AM. J. OBST. & GYNEC.* 40: 791, 1940.
- Morton, D. G.: *California & West. Med.* 42: 345, 1935.
- Idem: *AM. J. OBST. & GYNEC.* 49: 19, 1945.
- Papanicolaou, G. N., and Traut, H. F.: *Diagnosis of Uterine Cancer by Vaginal Smear*, New York, 1943, Commonwealth Fund.
- Ries, E.: *Section Obst., Gynec. & Abd. Surg.* 164, 1913.
- Scheffey, L. C.: *Radiology* 40: 436, 1943.
- Idem: *J. A. M. A.* 127: 76, 1945.
- Schmitz, H. E., and Sheehan, J. F.: *Am. J. Roentgenol.* 45: 229, 1941.
- Shaw, W. F.: *Surg., Gynec. & Obst.* 64: 332, 1937.
- Taussig, F. J.: *Tr. Am. Gynec. Soc.* 61: 75, 1936.
- Idem: *AM. J. OBST. & GYNEC.* 45: 733, 1943.
- Idem: *AM. J. OBST. & GYNEC.* 17: 1, 1929.
- Ward, G. G.: *AM. J. OBST. & GYNEC.* 44: 303, 1942.
- Werder: *Am. J. Obst. N. Y.* 52: 700, 1905.
- Wertheim, E.: *Die Erweiterte Abdominale Operation bei Carcinoma Colli Uteri*, Berlin und Wien, 1911, Urban und Schwarzenberg.

THE CURABILITY OF GRANULOSA-CELL TUMORS

G. E. SEEGAR JONES, M.D., AND R. W. TE LINDE, M.D., BALTIMORE, MD.

(From the Department of Gynecology, Johns Hopkins Hospital and University)

AS GRANULOSA-CELL tumors have become more commonly recognized, it is apparent that the prognosis is more difficult to determine than formerly believed. It was at first thought that these tumors were benign. As the number of case reports multiplied and the follow-up studies were available, it became evident that the granulosa-cell tumor, although more benign than most other ovarian carcinomas, nevertheless carried with it a definite malignancy. The difficulty in the prognosis of the granulosa-cell tumor is further reflected by the wide variation of statements in the literature concerning its malignancy. The occurrence of malignancy among the granulosa-cell tumors is quoted by various authors as being as low as 10 per cent and as high as 55 per cent, with all intermediate gradations. The collection of adequate statistics on the malignancy of the granulosa-cell tumor is difficult as the incidence of late recurrence in this tumor group makes five- or even ten-year follow-up studies inadequate. This fact has been strikingly brought to our attention by the recent return of three patients to the gynecologic clinic, all having recurrent granulosa-cell tumors fifteen, sixteen, and nineteen years, respectively, after their original operation. These three cases are herein reported with accompanying photomicrographs of the original and the recurrent tumors.

CASE 1.—R. G., No. 182937, a 39-year-old Negro woman, was admitted to the Johns Hopkins Hospital, June 13, 1923, with the complaint of abdominal swelling and some loss of weight during the past six months. Her past history and family history, as far as could be determined, were noncontributory. She had been married nineteen years and had had three pregnancies, the youngest child being 11 years old. The onset of menstruation had been at the age of 14 years with a 21-day-interval and a duration of three to four days. The last menstrual period was May 3, and the previous one April 5. For the past six months, since the onset of the present illness, she had had intermenstrual bleeding and profuse leucorrhea.

On physical examination the temperature was 99° F., pulse 84, respiration 40, and blood pressure 125/70. The hemoglobin was 68 per cent and the white blood count 7,200. There were signs of a right hydrothorax; the abdomen was extremely distended, and a nodular tumor mass, reaching 10 cm. above the symphysis, could be palpated. No definite fluid wave could be made out, but the percussion note was flat over the entire abdomen except for a triangle in the epigastrium. A pelvic examination showed the external genitalia to be normal, the cervix low in the vaginal vault, small, conical, and firm. The fundus seemed to be continuous with the abdominal mass and neither ovary was palpated as such. An x-ray of the chest confirmed the diagnosis of right pleurisy with effusion.

On June 15, 1923, a paracentesis was done and 4,000 c.c. of fluid removed. Analysis showed the ascitic fluid to have a specific gravity of 1.020 and a 4 plus albumin; no tumor cells were seen on microscopic examination. The paracentesis was repeated on June 17 and again on June 18, with the removal of 4,000 c.c. of fluid each time. On June 19 a thoracentesis was performed and 1,000 c.c. of fluid removed; this procedure was repeated on June 24.

On June 30 a paracentesis was again done, with the removal this time of 7,500 c.c. of fluid. A definite tumor mass which filled the pelvis could now be palpated. The patient was therefore operated upon, July 3, and a bilateral salpingo-oophorectomy and hysterectomy performed. On opening the peritoneum, a tumor, arising from the right ovary and reaching almost to the umbilicus, was seen. The mass was free except for a few adhesions to the posterior aspect of the broad ligament. There were no peritoneal or visceral implants and no visible evidence of metastases to organs or lymphatics. The left ovary was small and appeared to be normal as did the uterus.

The gross pathologic examination showed a normal uterus measuring 7.5 by 3.5 cm. with a smooth endometrial lining. The right ovary was converted into a mass measuring 17 by 10 by 12 cm., of firm consistency throughout except for one small cystic area. The tumor was well encapsulated and had a smooth, glistening surface, free from adhesions. At one end the capsule had apparently been torn. On section, the growth was found to consist of friable tissue loosely held together by fibrous bands. There were numerous small cystic spaces from pin size to 2 cm. in diameter. The one larger cyst previously described was filled with blood. The left ovary was not remarkable.

The microscopic picture of this tumor was found to vary from that of a cylindroid granulosa-cell tumor to a microfollicular type (Fig. 1). It was a solid tumor composed of small cells with prominent, dark-staining nuclei and very little cytoplasm. In areas these cells were arranged in cords, giving the appearance which has been described as the moiré silk pattern. In other areas the cells were arranged in sheets with abortive follicle formation and occasional pseudo-Call-Exner bodies. The uterine endometrium was autolized. No microscopic description was therefore available. The pathologic diagnosis made at the original examination was carcinoma ovarii.

The postoperative course was uneventful. On discharge examination there was no evidence of a recurrence of the hydrothorax and the ascites which had recurred was found to be greatly diminished. There was a small cystic mass in the cul-de-sac of Douglas which was thought to be encapsulated ascitic fluid.

The patient was next seen in the accident room, Oct. 10, 1939. She was then 56 years old and presented signs and symptoms of an acute intestinal obstruction. For one year she had had chronic obstinate constipation. During the past five days she had suffered from diarrhea and intestinal cramps. In the four days just prior to her hospital admission she had had no bowel movements, and directly before admission had become distended and had begun to vomit. A physical examination revealed classic signs of intestinal obstruction, and a laparotomy was immediately performed. The abdomen was filled with bloody ascitic fluid; the pelvis was choked by a soft multinodular tumor mass suggesting carcinoma in its gross appearance; there were numerous peritoneal implants. A biopsy was performed and the obstructed loop of bowel released. Her postoperative course was uneventful and she was discharged to be followed in the tumor clinic.

Urinary estrogen determinations showed approximately 70 R.U./24 hours or 140 R.U./1 total estrogens.*

The microscopic picture of the tumor biopsy was that of an insular or diffuse granulosa-cell tumor (Fig. 2). The cellular morphology was much the same as seen in the original tumor, but there was a more marked tendency for the cells to grow in solid sheets. In a few areas the trabeculated cordlike growth of the cylindroid granulosa-cell tumor was approached, but no microfollicular areas were present, and pseudo-Call-Exner bodies were very rare.

*The estrogen determinations were made on total 24-hour urine collections. The urine was acidified to Congo red paper and extracted three times with butyl alcohol. The butyl alcohol was distilled to dryness under vacuum and the residue taken up in 0.1 N. sodium hydroxide. This solution was neutralized and then hydrolyzed by boiling 10 minutes with 15 vol. per cent concentrated hydrochloric acid. The hydrolyzed solution was cooled and extracted five times with ether. The ether extract was evaporated to about a 5 c.c. volume and 5 c.c. of olive oil added. The remainder of the ether was blown off and the oil solution was then ready for assay.

The assays were performed on adult castrate rats which were known to respond to one gamma of estrone with an estrous smear. A single injection was given and the rats were smeared after 48 hours. Six or eight rats were used on each assay depending upon the amount of estrogen present in the solution. Only full estrous smears were read as positive.



Fig. 1.—(Gyn. Path. No. 28681.) Low-power photomicrograph of original tumor removed from Case 1. This tumor shows areas typical of the cylindroid and microfollicular types of granulosa-cell tumor.



Fig. 2.—(Surg. Path. No. 75293.) Low-power photomicrograph of the biopsy removed from Case 1, sixteen years after the original operation. This tumor showed a more marked tendency to grow in solid sheets. However, there were definite cylindroid areas.

After a consultation in the tumor clinic, a course of x-ray therapy was given. She received 1,700 roentgen units through two 20 by 20 cm. portals at a skin target distance of 50 through a Thoreus filter (2 mm. Cu, 1 mm. Al). A 200-kv., 20-Ma. machine was used. Nine hundred roentgen units were given to a third portal, 15 by 15 cm., over the liver. The factors were the same as before. The entire course covered a period of three months.

When seen Jan. 31, 1940, there were no palpable abdominal masses and no ascites was present.

The patient remained free from symptoms until July 20, 1943, when she was again seen, complaining of generalized abdominal pain and anorexia of about one week's duration. The physical examination at this time showed recurrent abdominal and pelvic masses and ascites. A second course of x-ray therapy was deemed advisable, and from August 5 to October 12 she received a total of 1,000 roentgen units, using two pelvic portals, one anterior and one posterior, of 20 by 20 cm. each. The factors were 400 kv., 5 Ma. at 70 skin target distance, using a 3-mm. Cu and 1-mm. Al filter. There was no apparent improvement either symptomatically or objectively and the patient died at home May 18, 1944. No autopsy was obtained.

CASE 2.—E. D., No. 171029, a 56-year-old Negro woman, was admitted to the hospital, April 8, 1924, complaining of a painful swelling of the lower abdomen. Her family history and past history were unessential. She had been married thirty-three years and had one son aged 30 years. There had been one miscarriage at four months, two years after the birth of this baby and no subsequent pregnancies. Her menses had begun at the age of 15 years and had always been regular, appearing every twenty-eight days and lasting five to six days with moderate flow and no dysmenorrhea or leucorrhea. Two years before admission she had begun to have menses every two weeks, lasting from five to six days but with scanty flow. Her last menstrual period had begun on March 25, 1924. She dated her present illness to three years before when she first noticed a lump in her "stomach." For one year she had had bearing-down pains in the lower abdomen, and for the past six months had noted a rapid increase in the size of her abdomen.

On physical examination at the time of admission to the hospital, the hemoglobin was found to be 55 per cent; white blood cells, 5,140; temperature, 98° F., pulse, 80; and blood pressure 162/100. There was a large abdominal mass extending to within 2 finger-breadths of the costal margin on the right and into the hypochondrium, with a slightly lower limit on the left. The surface of this mass appeared to be nodular; however, in the right lower quadrant it was somewhat cystic to palpation. In the midline and to the left there was a firm mass corresponding to a uterus enlarged to about twice normal size. This mass was freely movable from side to side. The pelvic examination showed the external genitalia to be normal. The cervix pointed anteriorly and was located just behind the symphysis. It was soft and patulous in consistency. The mass described on abdominal examination was noted as possibly an enlarged, myomatous fundus, although it was stated that the right ovary could not be palpated. There was a cystic mass in the cul-de-sac and a small mass on the left which seemed to be the left ovary. Numerous nodules extended into the lateral pelvic walls.

A hysteromyomectomy, bilateral salpingectomy, right oophorectomy, and partial left oophorectomy were performed, April 8, 1924. The mass described in the physical examination was found to be a large multinodular ovarian cyst. It was not adherent and was easily removed; however, one thin-walled locule was ruptured in the process. Grossly, the growth was a nodular tumor of the right ovary, with solid and cystic areas measuring 30 cm. in diameter. The cysts were of various sizes and colors, some smooth-walled and others lined with papillary projecting nodules. Interspersed throughout the cystic spaces were many firm, solid areas. There was no invasion and in every place the tumor seemed to be encapsulated. It was apparently entirely removed. When the microscopic appearance of this tumor was reviewed, it was found to be a typical microfollicular type of granulosa-cell tumor (Fig. 3). There were solid areas of small cells with dark-staining nuclei and relatively little cytoplasm. These cells were arranged concentrically about small cystic

spaces containing a pink-staining fluid. Call-Exner bodies were numerous. The uterine endometrium showed a hyperplastic pattern. The microscopic diagnosis at the time of the original examination was carcinoma of the right ovary arising in a cystadenoma.

The patient was discharged from the hospital after an uneventful postoperative recovery. It was not deemed advisable to give her postoperative irradiation.

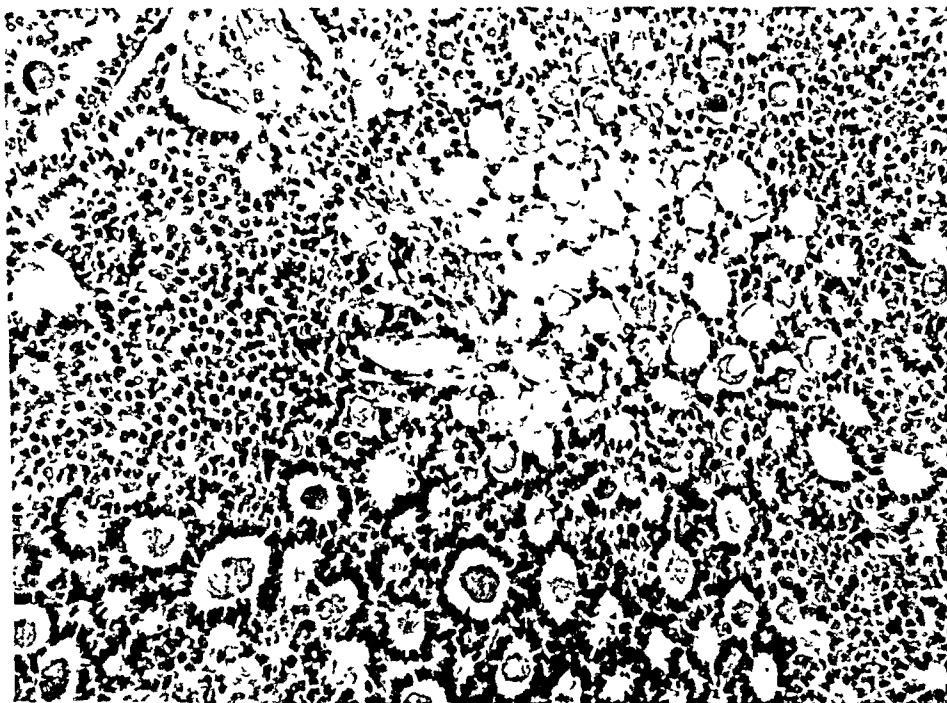


Fig. 3.—(Gyn. Path. No. 29319.) Low-power photomicrograph of original tumor from Case 2. The typical picture of the microfollicular granulosa-cell tumor is seen.



Fig. 4.—(Gyn. Path. No. 50609.) Low-power photomicrograph of the biopsy taken on Case 2, sixteen years after the original operation. The tumor again shows the typical picture of a microfollicular granulosa-cell tumor.

She was next seen June 1, 1938, at which time her only complaint was a painless "lump" in the "stomach" for one year. She was still actively employed as a cook and claimed to be in excellent health. She had never experienced menopausal symptoms and reported that she still maintained her libido. On physical examination the patient was found to be a small, well-preserved, vigorous Negro woman of 70 years. A mass, apparently originating in the pelvis and reaching to the umbilicus, was palpable. There were several small masses in the epigastric region, which were thought to represent liver metastasis. Two discrete nodules were palpable in the lower midline scar, measuring about 5 by 5 cm. in diameter. No ascites was demonstrated. The pelvis was choked by the tumor mass. The diagnosis of recurrent granulosa-cell tumor was made and at this time she was referred to the tumor clinic for advice as to x-ray therapy. Here it was felt that, in view of the apparent lack of symptoms and the questionable response of the granulosa-cell tumor to irradiation, the patient should not be treated. She was followed in the tumor clinic over a period of two years, during which time there was very little progress noted in the growth of the tumor masses. She was finally persuaded to enter the hospital for a biopsy of a tumor nodule. This was performed June 10, 1940, and urinary estrogen examinations were obtained concomitantly. The microscopic appearance of the biopsy was strikingly like that of the original tumor (Fig. 4). There were solid sheets of cells showing a tendency to form concentrically around small cystic spaces. Other areas approached the moiré silk appearance of the cylindroid granulosa-cell tumor.

The estrogen values in this case were calculated at approximately 500 rat units and 250 rat units of total estrogens per liter of urine. These values were obtained for specimens collected on two separate days. Unfortunately these were not calculated in terms of the twenty-four-hour period and so cannot be compared with the values obtained in the other two cases.

The patient continued to be seen in the dispensary every six months. She grew gradually more feeble and cachectic but never developed symptoms of acute intestinal obstruction. She remained fairly comfortable until her death, in September, 1942. The patient did not die in the hospital and no autopsy was obtained. As far as could be determined from the family, death was from inanition.

CASE 3.—L. M., No. 198364, a 26-year-old Negro woman, was admitted to the gynecologic ward, Oct. 30, 1920, complaining of an abdominal swelling and irregular menses. Her family history and past history were noncontributory. Menses had begun at 12 years of age and had been regular until about two years prior to her hospitalization. She had been married six years and had had four pregnancies, one normal delivery, one stillbirth, and two miscarriages, occurring in the order given.

The patient dated her present illness to about two years ago when she experienced a period of amenorrhea lasting about one and one-half years. In June, 1920, she began to bleed and continued to do so for three weeks with considerable loss of blood. In July, she bled about one week, approximately as profusely as a normal period, but following this she noticed some swelling of the abdomen and shortness of breath. She had no further vaginal bleeding until one week before entering the hospital. At this time she noticed a slight show of blood which continued until her hospital admission, Oct. 30, 1920.

On physical examination the blood pressure was found to be 135/95; white blood count, 8,000; red blood count, 3,500; hemoglobin, 45 per cent; and blood Wassermann, negative. The abdomen was markedly distended by an irregular mass which reached above the umbilicus but which could not be satisfactorily outlined because of the tenseness of the abdominal wall. There was marked bulging of the flanks, but no fluid wave could be elicited and the percussion note over the right flank was tympanitic. On vaginal examination the external genitalia were normal, the outlet was parous with good support, and Bartholin's and Skene's glands were negative. The cervix was small and firm, and visualization revealed no abnormalities. The uterus lay anteriorly and seemed to be somewhat enlarged. The tumor which had been felt on abdominal examination was found to arise in the pelvis and was thought to be ovarian in origin.

Operation was performed on Nov. 1, 1920. Following an escape of about 500 c.c. of bloody ascitic fluid, the tumor mass was readily visualized. It was purple in color, extremely vascular, and of a soft consistency. The growth was freely movable and was found to arise from, and entirely replace, the left ovary. The right tube and ovary appeared normal as

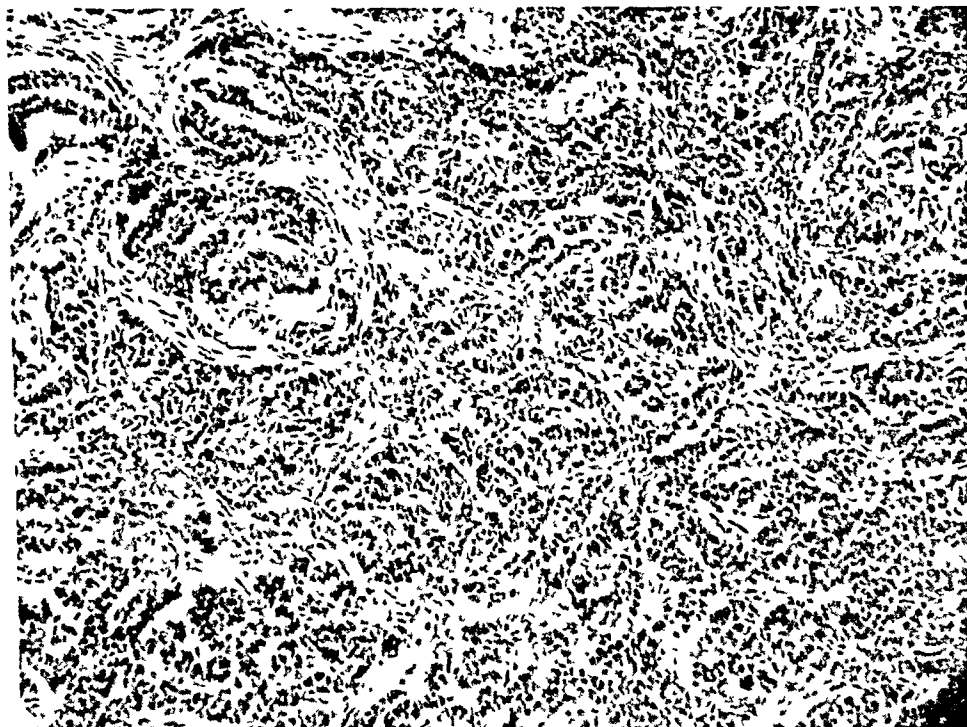


Fig. 5.—(Gyn. Path. No. 26320.) Low-power photomicrograph of the original tumor from Case 3. The cylindroid type of granulosa-cell tumor is seen.

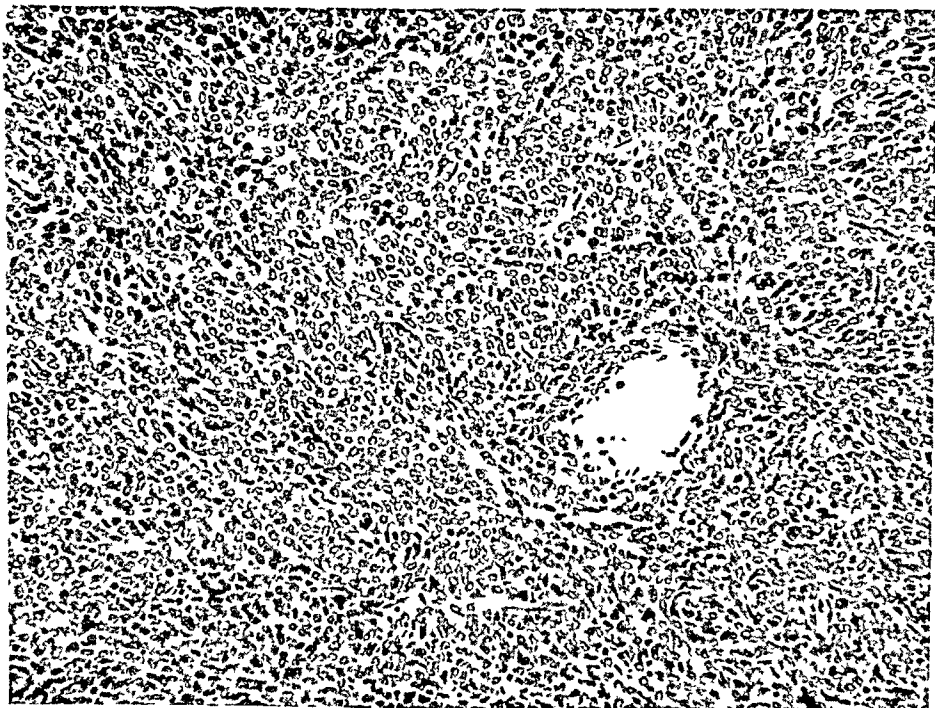


Fig. 6.—(Gyn. Path. No. 50505.) Low-power photomicrograph of the retroperitoneal tumor removed from Case 3, twenty years after the original operation. This tumor was very necrotic but the cellular area depicted represents the diffuse type of granulosa-cell tumor.

did the uterus except for a small myomatous nodule on the posterior surface. The tumor and the left tube were removed. No evidence of any ovarian tissue on the left side remained. The patient left the operating room in good condition, and the postoperative course was uneventful. She was discharged on Nov. 15, 1920, apparently well.

The pathologic report was as follows: The specimen was a tumor arising in and replacing entirely the left ovary, weighing 6,000 Gm. and measuring 28 by 25 by 15 cm. It had an irregular, nodular surface covered by a smooth, glistening capsule which was in no place broken. On section the growth was found to be in a large part solid with some cystic spaces. The solid areas were a mottled grayish-red in color and of soft consistency; it was trabeculated by fibrous tissue septa and there were numerous areas of degeneration. The cystic spaces contained clear fluid. The microscopic diagnosis at the time was adenocarcinoma in a multilocular cystadenoma. This tumor in retrospect was again found to have the morphology of a cylindroid granulosa-cell tumor (Fig. 5). It was largely a solid tumor composed of the small cell characteristic of the granulosa layer, arranged in cords running through a dense connective tissue stroma. In other areas these cells were in solid nests and in still others showed a tendency to form micro- and macrofollicular areas.

The patient was seen next in the dispensary in 1926, complaining of backache, and again in 1928 with a gastric disturbance. On neither occasion was there any evidence of recurrent disease in the pelvis.

On May 1, 1940, almost twenty years after her previous hospital admission, she was admitted to the medical service complaining of a "lump" in the right side. Three years previously her menstrual periods had ceased. One year ago she had noticed a slightly tender mass in the right upper quadrant near the umbilicus. This mass gradually increased in size until about three weeks before her admission to the hospital, at which time it began to grow rapidly. Six months ago her menstrual periods had recurred, and she had had periods of vaginal bleeding about every fourteen days since then. Three months ago she consulted her family physician because of a loss of 45 pounds in weight over a period of one year. She was told at this time that she had diabetes mellitus and was put on a diet but given no insulin.

At the time of admission her temperature was 99.6° F.; pulse, 100; respiration, 20; blood pressure, 180/100. The blood examination showed a white blood count of 9,800, and a hemoglobin of 90 per cent. The fasting blood sugar was 182 mg. per cent, and blood Wassermann was negative. The basal metabolic rate was +26 per cent. On physical examination the heart was found to be enlarged. The liver was palpated 3 fingerbreadths below the costal margin and there was a mass in the right upper quadrant which seemed to be continuous with the liver edge. The pelvic examination was negative except for the presence of a few myomatous nodules on the uterus. The diagnosis was thought to be hypertension, arteriosclerosis, diabetes mellitus, and an abdominal tumor. The blood estrogen was 40 R.U./1, and the urine estrogen, 35 R.U./24 hours, and 25 R.U./24 hours, on two separate days.

After several weeks of bed rest, an exploratory laparotomy was performed. The mass in the right upper quadrant was found to be a retroperitoneal tumor, and a careful examination of the abdomen and pelvis failed to reveal any other site of tumor formation. The uterus was enlarged and nodular, and the right ovary was small and fibrotic. No tumor was palpable in the gastrointestinal tract and the kidneys were normal. The tumor mass was shelled from its capsule with relative ease but at the end of the procedure a considerable amount of blood was seen to be oozing from the former tumor bed. This bleeding was controlled by packing with two gauze rolls which were left in place when the abdomen was closed. During the operation the patient's blood pressure, which had been 210/90, dropped to a systolic of 80, and, in spite of stimulants and supportive therapy of 500 c.c. of citrated blood, failed to sustain a rise. She died two hours after her return to the ward.

The tumor was fragmented when it reached the laboratory and numerous sections were taken in various locations. Many microscopic areas showed only hyalinized or necrotic tissue, but others showed solid islands of small cells with dark-staining nuclei and very

little cytoplasm, resembling those seen in the diffuse type of granulosa-cell tumor and approaching also the more cellular areas of the sarcomatous granulosa-cell tumor (Fig. 6). Microscopically this tumor was not as typical as the others in the group.

(Autopsy No. 16924.) At autopsy there was a small amount of serosanguineous fluid in the peritoneal cavity, and the gauze packs which had been left in place at the operation were saturated, but there was no free blood present. The abdominal viscera were grossly normal except for the liver which showed a marked compression of the right lobe. This was apparently caused by the right retroperitoneal tumor mass which had been removed at operation. The left lobe was correspondingly hypertrophied.

There was no evidence of malignant growth in the pelvis or pelvic organs. The uterus was irregularly enlarged and there were a few small myomatous nodules in the walls. The lining was smooth. The right ovary was pale and atrophic looking.

The hypophysis was slightly enlarged.

Microscopic examination of the organs showed an estrogenic type of endometrium, which corresponded to an interval nonsecretory pattern. The left ovary was senile in type; there were no Graafian follicles present. The pancreatic islands were increased in number but no hyalinization was present. There was some atrophy of the thyroid gland with an increase in the fibrous tissue stroma. The adrenals and pituitary gland were normal.

Discussion

The three cases reported further demonstrate that the prognosis in individual cases of granulosa-cell tumors is most uncertain. In all three cases the tumors were considered benign at the original operation in spite of excessive fluid being present in the abdomen in two. They were well encapsulated and there was no evidence of metastasis or implantation; in only one case (Case 2) was there a rupture of a small cystic locule with the escape of serous fluid—a circumstance which might possibly be considered a factor in disseminating the process. All three patients were apparently well and healthy over a period of at least fifteen years, and yet all died of the disease eighteen, twenty, and twenty-one years, respectively, after the original operation.

Whether the second tumors represent true recurrences or are new neoplasms is an interesting theoretical question and one with some practical significance, as its solution might give us a clue as to the best method of treatment. If they are metastases or recurrences, then the first operation should be as extensive as possible and great care should be taken in handling the tumors in order to avoid rupture. If they represent new tumors and can occur anywhere in the pelvis, or indeed in the abdomen, where embryonic rests might remain, a simple excision of the original tumor might be as satisfactory as a more extensive procedure.

In Case 1, widespread metastases occurred after sixteen years in spite of a bilateral salpingo-oophorectomy and a hysterectomy. In Case 3, in which only a unilateral salpingo-oophorectomy was done, the second tumor was located in the right retroperitoneal space, leaving the remaining pelvic organs free. This corresponds to a case reported by Compton of a recurrent granulosa-cell tumor in the right vesicouterine fold, completely independent of the right ovary, sixteen years after the removal of the original left ovarian tumor. Such cases make it impossible to be didactic about the treatment of granulosa-cell tumors and lead us to the very pessimistic conclusion that, in certain in-

stances, no operative procedure, no matter how extensive, will assure the patient freedom from the disease later in life.

The urinary estrogen values on the cases reported were within the limits of normal values for cyclic women except for one value of 500 R.U./1, which is high. All of the values, however, were elevated for postmenopausal women as, in the departmental laboratory, values above 10 R.U./24 hours or 15 R.U./1 for such patients are unusual. Such relatively low values may indicate that there is a wide variation in the ability of granulosa-cell tumors to secrete estrogens. Although excessive amounts of estrogens were not produced, clinically physiologic estrogenic effects were manifested. In Cases 1 and 2, in which the uteri had been removed, the vaginae exhibited no evidence of senile changes: the mucosa of each was succulent and the rugae well formed. In Case 3, there had been a recurrence of uterine bleeding and the endometrium at autopsy showed an estrogenic pattern approaching a true hyperplasia.

Conclusions

1. Three cases of granulosa-cell tumors have been reported in which recurrences developed not less than fourteen years after the original operation.

2. All three patients have died, eighteen, twenty, and twenty-one years, respectively, following the removal of the primary tumor, in spite of the fact that the tumors were well encapsulated and showed no evidence of metastasis or implantation at the original operation. One case recurred in spite of a bilateral salpingo-oophorectomy and a hysterectomy.

3. One case, No. 3, with widespread inoperable abdominal metastases, responded well to deep x-ray therapy over a period of three years but a subsequent recurrence of the growth proved refractory to treatment.

4. Total urinary estrogen values were not extremely high in two cases but within the range of values for normal cyclic women. However, the values were well above those usually found in this laboratory for postmenopausal women, into which age group all three patients fell at the time of recurrence. All three cases exhibited clinical signs of estrogenic activity on recurrence of the tumor.

References

1. Dockerty, M. B., and MacCarty, W. C.: *AM. J. OBST. & GYNEC.* 37: 425, 1939.
2. Compton, B. C.: *AM. J. OBST. & GYNEC.* 34: 85, 1937.

DIET REGULATION AND CONTROLLED WEIGHT IN PREGNANCY

WILLIAM J. DIECKMANN, M.D., DOROTHEA F. TURNER, M.S., AND
BARBARA A. RUBY,* S.B., CHICAGO, ILL.

*(From the Department of Obstetrics and Gynecology, and the Department of Internal Medicine
of The University of Chicago and the Chicago Lying-in Hospital)*

DURING the past fifteen years a number of reports on the value of diet in pregnancy have been published. Most of the authors have been very conservative in their conclusions as to the value of diet in pregnancy. However, some have made extravagant claims as to the value of an "adequate" or "complemented" diet in pregnancy. According to these authors, some of the results of a proper diet are to either prevent or decrease the incidence of abortion, anemia, toxemia, prematurity, fetal abnormalities, stillbirths and neonatal deaths, and to increase the ability of the mother to nurse her baby.

We believe that a diet containing sufficient amounts of the essential foods, especially protein, vitamins, and minerals, will lower the incidence of anemia in pregnancy and, by placing the woman in a state of nutritive efficiency, increase the resistance to infection which may occur during pregnancy or the puerperium, and also reduce the amount of edema in certain types of toxemia through weight control. We do not know whether or not such a diet will have any or all of the results mentioned in the preceding paragraph and believe that more extensive studies are necessary before we make the changes in our prenatal care indicated by these diet studies. Prenatal care both in private and clinic practice is already very expensive. However, its value does not compare with good delivery care. It is not the actual number of prenatal visits made by the patient that are of value but how carefully the doctor evaluates the findings and institutes the proper treatment that are of importance.

If each patient is to be interviewed repeatedly by a dietitian, the cost of prenatal care will be increased. We admit an average of 266 new obstetric patients to our clinics each month and two dietitians should be available for proper supervision. Also, the cost to the patient may be increased. The cost of additional food for normal pregnancy diet was approximately \$4.50 per month during the month of March, 1945, according to a report from the Home Economics Division of the Chicago Welfare Administration. Soldiers' and sailors' wives are given an allotment of \$50.00 per month, but if they become pregnant no increase is given for the additional food presumably required by the pregnant woman. It is surprising that the Children's Bureau has not made provisions for this additional cost. The Home Economics Division of the City of Chicago Welfare Administration calculated that the minimal cost for food for

*The service of the dietitian is supported by a special grant from the Community Fund of Chicago, Inc., as part of the clinic nutrition project in which twelve clinics are participating. The nutrition project was planned by the Health Division of the Council of Social Agencies of Chicago.

TABLE I. CHICAGO LYING-IN HOSPITAL STATISTICS

DELIVERIES	HOSPITAL MORTALITY					TOXEMIA (%)	ECLAMPSIA (%) (NO.)	
	MATERNAL (%) (NO.)		TOTAL FETAL (400+ GM.) RATE PER 1,000 BIRTHS		ABORTION (%)			
			STILL- BIRTHS	NEO- NATAL				
1931-1941—27,321	0.177	(50)	22.6	20.3	4.2	8.6	0.28	(78)
1941-1942— 3,276	0.122	(4)	18.3	16.8		7.7+	0.15	(5)
1942-1943— 3,813	0.105	(4)	19.6	17.0		6.9+	0.05	(2)
1943-1944— 3,481	0.057	(2)	16.2	16.5	4.8	6.6+	0.03	(1)
1944-1945— 3,471	0	(0)	12.4	17.0	7.2	6.1+	0.03	(1)

Toxemia figures since 1941 have not been completely tabulated.

a pregnant woman living alone was \$19.20 during the month of March, 1945. While the recommended foods are available and a market order may be given to facilitate purchasing, it cannot be expected that all patients will actually purchase the food recommended for this sum.

It is not our purpose to detract from the value of the previous reports but to examine them critically and to show that there are certain facts about obstetric statistics as well as about diet that must be kept in mind by anyone attempting to draw conclusions based on so many variables. For example, during the past year no maternal deaths occurred in our Service. Our dietitian has been advising patients during this period and one could attribute the lack of maternal deaths to this factor alone. We are quite certain that no one would be so rash.

Data in Table I list statistics from our hospital for some maternal and fetal conditions. These statistics over a period of years have shown marked decreases in the incidence of eclampsia and severe pre-eclampsia, in maternal and fetal mortality, and in other complications. We attribute these reductions to increased skill and knowledge of the staff and better supervision of the resident staff. If we compare our results for the past year with those of ten years ago, the differences are marked. Control groups must be large and must be watched as carefully as the experimental groups and by the *same* individuals.

The increased number of abortions on our service during the past two years is due to the inclusion of all incomplete abortions (formerly, only those patients who passed the fetus in the hospital were counted). The incidence is still less than the average reported in the literature because even if the patient is seen at six to eight weeks' gestation (which is very early) and aborts, but does not enter the hospital, no notation is made in the hospital statistics.

Data from some of the nutritional reports are listed in Table II. Attention is directed to the small number of patients in most of the groups, and yet conclusions are based upon these small groups which, if acted upon, would raise the cost of prenatal care. Where lives are concerned, cost should not be considered; but we have not reached that period in medicine in which cost is of no importance.

A preliminary report by the British Minister of Health in 1938 stated that among 4,446 mothers receiving special food, the puerperal death rate was 0.45 per cent; the maternal death rate from associated causes, 0.67 per cent; and the infant death rate (stillbirth and neonatal),

5.4 per cent. Among 9,040 mothers not receiving special foods, the corresponding rates were 3.54, 1.33 and 8.3 per cent, respectively. Unfortunately, the Minister in a later note stated that the practical difficulties in the way of securing precise comparability between the contrasted groups are so great that it is unlikely that scientifically adequate conclusions could be reached.

The People's League of Health in England studied large groups of pregnant patients, giving the study group vitamins and minerals. The results reported in 1942 are listed in Table II. The decrease in the incidence of toxemia was not significant but it was for pre-eclampsia. A significant decrease in the premature delivery rate was noted (before the fortieth week). These latter figures would have more value had they been divided into periods, i.e., before 28 weeks, and 28 to 38 weeks.

Balfour reported in 1944 on the results of complementing the diet of large numbers of pregnant women in England and Wales with yeast and milk. The results are given in Table II. They show a significant decrease in the total fetal mortality for the study group. One wonders about the difference in fetal mortality in the control groups from neighboring towns, ranging from 63 to 96 per 1,000 births, and the high maternal mortality due to toxemia.

Tompkins stated that the incidence of toxemia was almost seven times greater in patients on a deficient diet. The stillbirth and neonatal rates were also much higher. His results, which he attributes to diet, would be far more significant if he had obtained diet records and given prenatal care to his control patients instead of selecting their histories from the hospital files.

The report by Burke and her co-workers is difficult to break down into the number of various complications. One wonders why there were no abortions in this study. All stillbirths, premature and functionally immature fetuses, babies with erythroblastosis, congenital heart and other anomalies, are classified in the "poorest infant" group. There were four patients with placenta previa with no fetal deaths, but if the series were larger there would be fetal deaths from placenta previa, from abruptio placentae, and from the accidents of labor which certainly cannot be charged to diet. The groups of good-excellent and poor diet are too small to warrant any conclusions. The fetal grouping is not warranted.

Burke and co-workers state: "Nutrition has not occupied a place of major importance as a part of prenatal care. The obstetrician's primary interest is not so much the health and development of the unborn infant as the health of the mother during pregnancy." Diet instruction, right or wrong, has been given by obstetricians to pregnant patients for over thirty years. The obstetrician is interested in having a live healthy mother and a live healthy baby. If he disregarded one or the other he would soon have no practice.

Extravagant claims had been made by several investigators relative to the decrease in fetal mortality in the hemorrhagic disease and intracranial injury group, resulting from the administration of vitamin K to the mother during labor. Potter compared the stillbirth and neonatal deaths and autopsy findings on our service for five consecutive years. The data are given in Table III.

TABLE III

	1940	1941*	1942*	1943	1944 (10 MONTHS)
Stillbirth	24.6	19.4	20.6	15.6	14.3
Neonatal	26.4	16.8	18.0	15.9	17.5
Total	51.0	36.2	38.6	31.5	31.8
Number of babies	2,710	3,093	3,517	3,768	3,475

*Parenteral injection 3.2 mg. vitamin K (2-methyl-1, 4-naphthohydroquinone, 3-sodium sulfonate) during labor.

Dr. Potter states: "Examination of the death rates for the two years during which vitamin K was given and for the following two years show almost identical rates for the first ten days of life, and a distinctly lower stillbirth rate in the control series." Had the rate

for 1940 been used as a control, the improvement would have been marked. Potter concludes: "From a study of this material it seems justifiable to conclude that the routine administration of vitamin K during labor in no way affected the infant mortality or stillbirth rate in the Chicago Lying-in Hospital."

Abortion.—According to Taussig, the incidence of abortion ranges from 10 to 40 per cent of all conceptions. The figures for our clinic are 5.6+ per cent. Mall, Streeter, Huntington, and Hertig have each reported that two-thirds of spontaneous abortions are associated with and probably due to extensive abnormalities of the fetus. The remainder are due to maternal causes, such as: anomalies of the uterus, tumors, systemic disease, abnormal implantations of the ovum, etc. Improper diet may be an important factor in the etiology of these causes, but positive proof is lacking. Dieckmann and co-workers reported that in their diet studies in pregnant patients, 2.4 per cent of the control group aborted; and none aborted in the three complemented diet groups (cereal; vitamins A and D; both). Since most abortions occur within the first three months, and since most patients do not come to the doctor until after the third month, it is obvious why most diet studies have such a low incidence of abortion.

Toxemia.—The incidence of toxemia varies throughout the United States (0.5 to 25 per cent) and throughout the world (0 to 28 per cent). The edema, proteinuria, hypertension, and associated symptoms may be due to pre-eclampsia, eclampsia; essential hypertension, or glomerular nephritis (acute or chronic). Our percentages for these conditions are 38, 4, 56, and 2 per cent, respectively. The average fetal mortality due to toxemia from various clinics is 16 per cent (9 to 26 per cent). Our fetal mortality is given in Table IV.

TABLE IV		
TOTAL FETAL MORTALITY		
(%)		
Pre-eclampsia:	mild	6
	severe	17
Essential hypertension:	mild	7
	severe	27
Glomerulonephritis		58

Obviously, the fetal mortality depends on the type of toxemia and on the severity. Pre-eclampsia occurs most frequently in the first pregnancy and diet is certainly one factor. The fact that it rarely recurs indicates that there are other factors because the diet would in all probability be the same in subsequent pregnancies. Fetal death in patients with essential hypertension and glomerulonephritis is due to vascular lesions in the maternal placental vessels and it is difficult to conceive of any effect that diet could have on these vessels. There is a very definite connection between the incidence of toxemia and civilization. Eclampsia and pre-eclampsia either do not occur or are very rare in many native peoples. Dieckmann and co-workers reported that, in their complemented diet studies, two groups showed a significant decrease in the incidence of toxemia and one showed an increase. They attributed these inconsistent results to the small number of patients in each group.

Anemia.—The hemoglobin concentration is decreased in normal pregnancy, reaching a minimum figure at 26 to 34 weeks' gestation and then increasing, but not reaching nonpregnant values until some weeks post partum. If one uses nonpregnant standards, two-thirds of the pregnant patients are anemic. If one uses pregnant standards, 12 per cent of pregnant patients are anemic. Bethell has shown that if the pregnant patient has an intake of 50 grams or more of animal protein per day, the patient will not develop macrocytic anemia during pregnancy.

Hemorrhages.—Most dietary reports have not discriminated between the various types of hemorrhage occurring in pregnancy. Since the hemorrhage in placenta previa is the result of an abnormal implantation of the ovum, it is difficult to see how diet could play any part. The majority of the cases of abruptio placentae are associated with toxemia, and it is conceivable that the toxemia could be attributable to diet. However, these patients usually have essential hypertension, rarely pre-eclampsia.

Fetal Mortality.—Our uncorrected figures for stillbirths (400 Gm. +) for a ten-year period was 2.26, and for the past year 1.24 per cent. It is 0.92 per cent for fetuses weighing 1,500 Gm. or more. Similar figures for the neonatal mortality are 2.03, 1.70, and 1.2 per cent. In 51 per cent of the stillbirths and in 19 per cent of the neonatal deaths, it was impossible for either the obstetrician or the fetal pathologist to determine the cause of death. It is difficult to see how a proper diet could be an important factor in reducing stillbirths and neonatal deaths. If there is a constant decline in the fetal mortality, as is occurring on our Service, and if the percentages are small, it is obvious that great care must be used in the interpretation of results, even though the differences may be statistically significant.

Fetal Anomalies.—Animal experimentation has demonstrated that *extreme* diet deficiencies result in some animal species in fetal abnormalities. Heredity is still the important factor in the production of minor abnormalities (cleft palate, extra digits, etc.) in human fetuses. Major anomalies have an unknown etiology. Burke and co-workers attribute fetal abnormalities in the human being to diet deficiency although their group is extremely small.

Size of Baby.—The veterinarian has been able by selective breeding and diet to increase the weight and stature of various animals, but heredity is still the important governing factor. Burke and co-workers believe that they have been able to increase the weight and length of the baby by increasing the protein intake. One wonders whether, if the protein intake in their patients had been increased another 20 or 30 grams per day, the fetal length would have increased an additional 2 or 3 centimeters.

Skeleton and Teeth.—A marked and prolonged deficiency in calcium, phosphorus, and vitamin D before and during pregnancy will result in fetal rickets and in faulty fetal tooth development, as well as in osteomalacia in the mother.

Breast Milk.—The veterinarian has been able by careful selective breeding and diet controls of cattle to increase either the amount or fat content of milk. This has not been done in the human being. However, the quality of human milk has been shown to be affected by a deficient diet. The percentage of mothers

with adequate breast milk at discharge from maternity hospitals is disappointingly low, due in great part to lack of nursing care. Most obstetricians believe that if the patient had a proper diet during pregnancy and lactation and if adequate time for instruction in nursing and psychotherapy could be given by the nurses to each mother, three-fourths of the babies instead of less than half would be breast fed.

Weight.—We believe that the pregnant patient must have a proper diet, but this does not mean that she should have an unlimited caloric intake and as a result gain excessively in weight. The pregnant patient does not have to eat for two her own size. The diet must be increased during the last trimester. Data shown in Fig. 1 are taken from a report by Swanson and Iob who analyzed fetuses at various ages. It is obvious that the amounts of nitrogen, calcium, phosphorus, and iron required for fetal growth are minimal up to the twenty-eighth week and from then on increase markedly; but even at term the total amount required is not excessive. The figure also shows the average weight of the baby for the various calendar months and it is noteworthy that the fetus at twenty-eight weeks weighs only 1,045 grams. We believe that the pregnant patients should be fed in only needed amounts as an athlete is fed at the "training table"—not stuffed as if for a killing.

It should be noted that many of the diseases peculiar to pregnancy occurring in domestic animals are the result of civilization and/or overfeeding. The milk fever of cattle occurs only in thoroughbred stock and is due to the marked loss of calcium in the milk. A disease of pregnant ewes is due to overfeeding and lack of exercise. The same is true for rabbits.

Chesley has made an extensive study of weight changes in pregnancy and states that the average weight gain based on all the reports in the literature is 10.9 kilograms with a standard deviation of 4.9 kilograms.

I calculated in 1936 that the necessary weight gain due to the physiologic changes of pregnancy—fetus, placenta, amniotic fluid, uterus, blood volume, breasts, etc.—amounts to 6.7 kilograms. Chesley calculates from reports in the literature a gain of 6.2 kilograms for the same physiologic changes of pregnancy. He states that there is an additional gain of 7 kilograms for the patient's body and tissues, of which approximately 2 kilograms are due to stored nitrogen. We do not see any need for the additional 7-kilogram gain and are not certain what levels of nitrogen storage are necessary. We believe that there is no need for a total weight gain greater than 8 kilograms above the ideal weight. The first three months of pregnancy are characterized by either little gain or a loss of weight. The average weight gain for the remainder should then be a maximum of 225 grams ($\frac{1}{2}$ pound) per week.

Every patient whose total weight gain is over 10.9 kilograms does not necessarily have toxemia. Statistics do show, however, that the incidence of toxemia is increased in those patients who gain more than 13 kilograms. The total gain in pregnancy is not so important as the rate of gain. Patients who gain more than 0.6 kilograms per week have an increased incidence of toxemia, especially pre-eclampsia.

Bethell and co-workers state that with nutrition instruction a much smaller percentage of patients were overweight at term. One year later a considerably higher percentage were overweight, having paid no attention to diet in the interim. They also state that of most significance for the majority of overweight women is the fact that *pregnancy is the provocative or aggravating agent responsible for increased weight gains throughout life, leading to the well-known hazards of obesity in later years.*

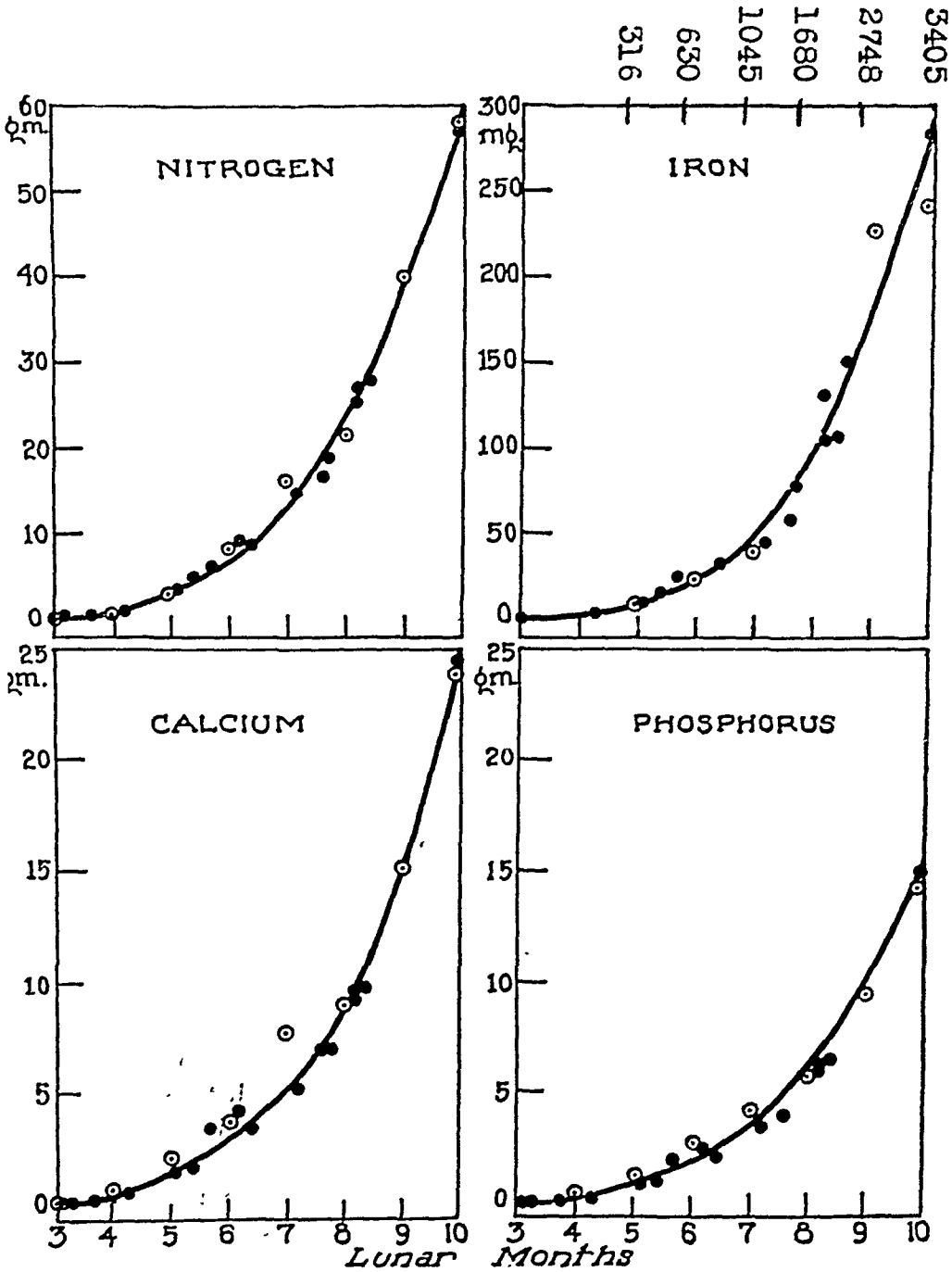


Fig. 1.—Shows the content of nitrogen, calcium, phosphorus, and iron, and weight of the fetus from the third to the end of the tenth lunar month. In all of the curves the authors' data are represented by the solid dot. (Modified from Swanson and Job: AM. J. OBST. & GYN. 38: 382, 1939.)

If the patient's weight is ideal before pregnancy, we believe that the maximum gain should be 7 to 8 kilograms. In order to aid the patient in limiting her weight gain, suitable dietary instructions have been developed. In the organization of a plan for practical use, a procedure has been developed whereby

TABLE V. APPROXIMATE EVALUATION^a OF DAILY PLAN OF FOOD INTAKE FOR PREGNANCY, CONTAINING 1,800 CALORIES

DAILY FOOD INTAKE	QUANTITY		MINERALS		VITAMINS					FOODSTUFFS			CALORIES ^b
	WEIGHT (GM.)	APPROXIMATE MEASURE	Ca (G.M.)	Fe (MG.)	A (I.U.)	ASCORBIC ACID (MG.)	THIAMINE (MG.)	RIBOFLAVIN (MG.)	NIACIN (MG.)	CARB. (GM.)	PRO. (GM.)	FAT (GM.)	
Milk	960	1 quart	1.12	2.0	1,640	8	0.40	1.72	1.2	48	34	36	640
Egg	50	1 medium	0.03	1.4	495		0.07	0.18			6	6	80
Meat, poultry, ^c or fish, cooked	100 ^d	Raw weight 4 oz.	0.01	3.3	2,807	2	0.28	0.37	5.9	1	24	13	215
Bread, whole grain or enriched	90	3 slices	0.03	2.0			0.24	0.13	2.6	45	9	3	240
Potato, cooked	100	$\frac{1}{2}$ cup	0.01	0.7	35	8	0.08	0.03	1.0	19	2		85
Green or yellow vegetable ^e	100	1 serving	0.10	1.4	4,870	23	0.05	0.17	0.6	6	1		30
Other vegetable ^f	200	2 servings	0.06	0.8	405	10	0.08	0.07	0.6	10	2		50
Legumes or beans: peas, navy, kidney, lima, or soybeans, or peanut butter	100 50 25	$\frac{1}{2}$ cup cooked $\frac{1}{4}$ cup 1 $\frac{1}{2}$ table-spoons	0.03	2.4	20		0.14	0.06	1.8	19	7	3	130
Citrus fruit	200	1 cup juice											
Other fruits	100	1 serving											
Butter or enriched margarine	15	3 level tea-spoons		0.6	161	5	0.05	0.05	0.4	15	1	12	65
Coffee	25	2 table-spoons			480								110
Sugar	15	1 table-spoon					0.04	0.01	2.3				
Vitamin D concentrate ^h										15			60
Total			1.45	15.4	11,273	140	1.57	2.85	16.8	200	88	73	1,800

^aFigures on nutritive content taken from "Food Composition Table for Short Method of Dietary Analysis (Revised)" by Eva G. Donelson and Jane M. Leichsenring, J. Am. Dietet. A. 21: 440, 1945; and "Tables of Food Composition Giving Proximate Mineral and Vitamin Components of Foods," and "Tables of Vitamin Losses in Cooking of Foods," Committee on Food Composition of Food and Nutrition Board, National Research Council, 1944.

^bCalories have been rounded off to nearest 5.

^cThe evaluation of meat is based on the use of 100 grams of liver, 250 grams of pork or ham, 150 grams of fish, and 500 grams of beef, veal, lamb, or fowl per ten-day period.

^dWeight after cooking.

^eThe vegetables included in this group are asparagus, broccoli, carrots, green beans, kale, spinach, turnip greens, and other greens.

^fThe vegetables included in this group are: tomato, fresh, canned, or juice; vegetables commonly served raw as celery, cucumber, lettuce, and cabbage; and other cooked vegetables as beets, eggplant, onions, rutabagas, and cauliflower.

^gAll fruits except citrus have been included in this average.

^h400 to 800 I. U. of vitamin D are given, the actual amount depending upon the concentrate used.

it is possible to note the value and use of each food which composes a plan of daily food intake containing 1,800 calories. By making appropriate adaptations of this basic plan, it then becomes possible to formulate diets suitable for variations in size, age, activity, cost, and food habits. In all cases, however, an attempt is made to limit the weight gain. The daily plan of food intake containing 1,800 calories is enumerated and evaluated in Table V.

In view of the present rationing restrictions and food shortages, complete instructions concerning food alternates have been necessary, particularly for the protein-containing foods. The restrictions on fat have been more of an advantage than a disadvantage because of the need for caloric limitations. Table VI outlines some of the suggestions given as alternates for the protein-containing foods.

TABLE VI. PROTEIN ALTERNATES RECOMMENDED IN DIET FOR PREGNANCY

DAILY FOOD INTAKE	APPROXIMATION OF PROTEIN CONTENT (GM.)
32 oz. (1 quart) of fluid milk	34
The approximate protein equivalent of 1 pint of fluid milk is 8 oz. of evaporated milk or 1½ oz. (5 level tablespoons) of dried skim milk. Also, 1 serving (4 oz.) of milk pudding* or ice cream* may be considered approximately equivalent to 3 oz. of fluid milk.	
One egg or 1 oz. of American cheddar-type cheese or 1 oz. of cottage cheese or 1 oz. of fish, poultry, or meat, or 1½ tablespoons of peanut butter†	6
4 oz. serving of meat or poultry or fish, or 2 oz. of soybean flour, or 7 oz. (1 cup) cooked soybeans, or 2 eggs and 2 oz. of cottage cheese. Also, 1½ tablespoons peanut butter may be considered equal to 1 oz. of meat.	24
3½ oz. serving (½ cup) of cooked peas, navy beans, kidney beans, or lima beans, or ¼ cup cooked soybeans, or 1½ tablespoons peanut butter	7
3½ oz. serving of potato, cooked	2
Other vegetables—3 servings	3
Citrus fruits—2 servings and one other fruit	3
3 slices of bread, enriched or whole grain, or equivalent grain product	9
The approximate protein equivalent of one slice of bread is 1 oz. (dry weight) of cereal or ½ cup cooked spaghetti* or noodles* or 6 soda crackers, or 1 small piece of cake,* or a 2 inch cube of cornbread,* or 3 graham crackers.	
Total	88

*Where variations in caloric values occur, adjustments are made to maintain isocaloric values.

†Twelve grams of dried brewer's yeast (3 level teaspoons) or twelve grams of peanut flour also yield six grams of protein.

When the patient is not accustomed to drinking milk, recommendations may be made, as suggested by Turner, for "the use of milk in soups, desserts, or flavored beverages. However, the most inconspicuous and in many cases, the most acceptable way in which to add milk is in the form of dried milk. Approximately 1½ ounces (5 tablespoons) of dried skim milk will equal one pint of fluid milk. This dried milk may be incorporated as a dry ingredient in the preparation of meat loaf, mashed potato, sandwich spreads, cooked cereals, hot breads, cookies, pastries, or puddings with little difficulty. Also, a palatable drink may be prepared by adding approximately 2½ tablespoons of dried milk to one glass (8 oz.) of fluid milk. This will provide approximately 15 Gm. of high quality protein per glass. In some parts of the country, dried milk may be obtained from the retail grocery store. In other places it may be necessary to depend on the courtesy of a bakery shop, hospital, or dairy."

Turner also pointed out that "milk contributes the major portion of calcium and phosphorus in the diet as well as a large share of the protein and vitamins of the B complex.

While 2½ ounces of cottage cheese would be equivalent in protein content to one pint of milk, the cottage cheese would supply less than one-tenth of the calcium, phosphorus, iron, vitamin A, thiamine, and riboflavin supplied by the milk. Two and one-half ounces of American cheddar cheese would supply calcium equivalent to one pint of milk but would be much lower in vitamins of the B complex. In this case, the further use of liver or other glandular meat one or two times a week would be desirable to augment the iron and A and B vitamins in the diet. Pork would enrich the thiamine intake. Eggs will supply a significant amount of vitamin A and iron. Legumes and whole grains will also contribute iron and vitamins of the B complex." A comparison of the nutrients in equivalent amounts of protein-containing foods may be found in the table by Turner. Where any alternates or substitutions are used on the basic plan of food intake an attempt must be made to compensate for all nutrients.

The normal pregnancy diet as discussed is presented to the patient either in class or in an individual interview. Because of the large number of patients in the clinic, no attempt has been made to follow up these instructions unless the patient needs additional help in making certain dietary restrictions. The dietitian is always available for consultation with patients.

Lactation.—The increased requirements for lactation, over the needs for pregnancy, may be met simply by including an additional pint of fluid milk or equivalent (see Table VI), an additional serving of citrus fruit, and two tablespoons peanut butter or equivalent. Other foods may be used to supply these increased needs, by considering the total nutrient content of each food and making adequate use of compensatory foods.

We plan to make an evaluation of the dietary instruction by an intensive study of a part of this group of patients, through a correlation of the dietary intake with the laboratory and clinical findings. In an effort to increase the reliability of the diet history, it is planned to make a periodic record of the weight of the patient's food intake. It should then be possible with corresponding laboratory and clinical findings to determine if a correlation exists between nutrition and the incidence of toxemia, anemia, and the other factors previously mentioned.

Summary

The relation between diet in pregnancy and maternal and fetal complications and mortality has been discussed. The data so far reported in the literature indicate the value of a proper diet. The results, if true, are of the greatest importance, but the number of cases in each series is small. Furthermore, some of the conclusions are at variance with clinical obstetrics. The cost of supervising pregnant patients as well as supplying diet deficiencies would be increased but would be justified if the reports are confirmed. Therefore, we believe that research projects in maternal nutrition should be started in various clinics throughout the country so that in a short period of time sufficient material will be available.

We are limiting the total gain above the ideal weight to a maximum of 8 kilograms by restricting the caloric content of the pregnancy diet.

References

- Balfour, M. I.: *Lancet* 1: 208, 1944.
- Bethell, F. H., and Blecha, E.: *Clinics* 1: 346, 1942.
- Bethell, F. H., Blecha, E., and Van Sant, J. H.: *J. Am. Dietet. A.* 19: 165, 1943.
- Burke, B. S., Harding, V. V., and Stuart, H. C.: *J. Pediat.* 23: 506, 1943.

- Burke, B. S.: *Milbank Mem. Fund Quart.* 23: 54, 1945.
- Burke, B. S.: *J. Am. Dietet. A.* 20: 735, 1944.
- Burke, B. S., Beal, V. A., Kirkwood, S. B., and Stuart, H. C.: *AM. J. OBST. & GYNEC.* 46: 38, 1943.
- Burke, B. S., Beal, V. A., Kirkwood, S. B., and Stuart, H. C.: *J. Nutrition* 26: 569, 1943.
- Chesley, L. C.: *AM. J. OBST. & GYNEC.* 48: 565, 1944.
- Dieckmann, W. J.: *The Toxemias of Pregnancy*, St. Louis, 1941, The C. V. Mosby Co.
- Dieckmann, W. J., Adair, F. L., Michel, H., Kramer, S., et al.: *AM. J. OBST. & GYNEC.* 47: 357, 1944.
- Dieckmann, W. J., and Swanson, W. W.: *AM. J. OBST. & GYNEC.* 38: 523, 1939.
- Ebbs, J. H., Tisdall, F. F., and Scott, W. A.: *J. Nutrition* 22: 515, 1941.
- Ebbs, J. H., Brown, A., Tisdall, F. F., et al.: *Canad. M. A. J.* 46: 6, 1942.
- Ebbs, J. H., Scott, W. A., Tisdall, F. F., et al.: *Canad. M. A. J.* 46: 1, 1942.
- Hertig, A., and Sheldon, W.: *Ann. Surg.* 117: 596, 1943.
- Huntington, J. L.: *AM. J. OBST. & GYNEC.* 17: 32, 1929.
- Minister of Health, J. Roy. Inst. Pub. Health & Hyg. 1: 572, 1939.
- People's League of Health, Interim Report of: *Lancet* 2: 10, 1942.
- Potter, E. L.: *AM. J. OBST. & GYNEC.* 50: 235, 1945.
- Slonaker, J.: *Standford Univ. Publ.* 6: 320, 1939.
- Swanson, W. W., and Iob, Vivian: *AM. J. OBST. & GYNEC.* 38: 382, 1939.
- Taussig, F. J.: *Abortion*, St. Louis, 1936, The C. V. Mosby Co.
- Tompkins, W. T.: *J. Internat. Coll. Surgeons* 4: 147, 1941.
- Turner, D.: *J. A. M. A.* 128: 590, 1945.
- Williams, P. F.: *J. A. M. A.* 127: 1052, 1945.
- Williams, P. F.: *AM. J. OBST. & GYNEC.* 43: 1, 1942.
- Williams, P. F., and Fralin, F. G.: *AM. J. OBST. & GYNEC.* 44: 647, 1942.
- Workany, J., and Nelson, R.: *J. Nutrition* 23: 321, 1942.

GOVERNMENT AND MATERNAL WELFARE

FRED L. ADAIR, M.D., CHESTERTON, IND.

THE well-known phrases that each citizen of our country is guaranteed the fundamental rights of "life, liberty, and the pursuit of happiness," and that our government is "of the people, by the people, and for the people" are purposeless unless certain fundamental objectives are attained. Without a satisfactory economic base and a workable and responsive political and social system, these desiderata are not obtainable. Governmental authority must be derived from the people, be exercised by the people, and be for the benefit of the people.

Knowledge is the source of the power of the people and it must be based upon the truth. The fullness of life, the preservation of liberty, and the attainment of happiness depend upon education and health. These are very intimately interwoven. The meaning of these words is not to be interpreted in a narrow sense but broadly in their full application to body, mind, and soul. This cannot apply to the few if democracy is to succeed but must rest upon the freedom of equal opportunity for all to acquire the knowledge and health essential to their well-being. It must be recognized that, while each one of us is entitled to as nearly equal hereditary and environmental opportunities as it is possible to have, nevertheless we are not all alike in our bodily, mental, and spiritual powers. It is neither essential nor desirable that we should be, for life is too many-sided and complex for all of us to fit into the same groove. The comforts and pleasures of life are increased by the products derived from the diverse talents of others. However, we should have the personal optimum of knowledge and health to secure the maximal pleasure, happiness, and benefit from the manifold opportunities of life. Our Government can and should provide the opportunities, but the individual must supply the initiative, the time, the energy, and the ability. Unless these opportunities are forthcoming, it would seem that democracy could not succeed.

Our Government was founded upon the ideal of local self-government extended to progressively higher levels through systems of representation. The ideal would seem to be a maximum of local self-government with a minimum of centralized governmental control. In our extensive country with its great variation in available resources and wealth as well as in concentration and diversity of the population, there are manifold local problems which have to be solved largely by the intelligent interest of the local citizenry which frequently may need assistance from governmental agencies at higher levels.

The problems are not the same in all communities, and the methods of their solution differ. The abilities of the local leaders are not always equivalent. The total and the per capita cost would not be the same in every area even for identical plans. The available wealth also varies so that all communities would not be able to carry out programs to give their citizens the essentials of health and knowledge, and balance their budgets. This of course

means some assistance from outside. Other types of help would also be necessary as competent personnel must be available for various activities in devious capacities. All this implies the development and establishment of some plan for the equalization of the distribution of wealth and personnel so that these essential opportunities for the attainment of health and knowledge may be available for all.

Inasmuch as all of us are vitally affected by these programs, it behooves each one to scrutinize carefully all plans, especially those which involve our special activities and alter our ideals of democratic government. Various groups are particularly concerned, and it is important to recognize that the manner in which the individual is affected also is reflected in the group and reacts on the community for better or for worse. Those who are most familiar with the work of the groups in special fields should be the best informed and most capable of judging the results not only upon the workers themselves but also upon the segment of the community which they serve.

Before discussing problems concerning health it may be well to discuss those concerned with education because these have been more fully developed and determined on a national scale. We probably would all agree that in this field there has not been an equal opportunity for all of our prospective citizens. There are many factors which are responsible for this, one of which is the lack of sufficient wealth in some areas with which to provide the educational facilities and personnel. We have developed, side by side, a public school system, from preschool to higher levels of learning, and private and secular institutions with diverse means of support which meet a variety of needs and desires. All this has been accomplished through individual, local, and group initiative and enterprise, with a modicum of centralized governmental leadership or support. There are some serious gaps which need to be filled, many of which could be bridged by Federal, State, or local governmental subsidies.

A word about taxation may be pertinent. One could be justified in believing that two of the main purposes of Federal and State taxation should be: first, the support of the centralized government; and second, the equalization of the distribution of monies to secure to each community the essential opportunities to secure health and knowledge. This, according to our democratic principles, should be accomplished with a minimum of centralized control and a maximum of local initiative and accomplishment.

The development of health agencies is not exactly comparable to that of those devoted to education, as their local development has not been nearly as widespread. This is in part due to the more recent recognition of the essentiality of community health agencies. It appears that there is a much more pronounced tendency to centralized Federal initiative, support, and control through funds distributed to the States according to bureaucratic planning. It should be stressed that these tax funds come from the communities in varying ratios but are distributed mainly on the basis of matching and on a per capita basis. It is also important to recognize that of the total national income only a certain percentage could ever be available for taxation without wrecking our social and economic structure and, further, the larger the percentage

which goes into the Federal budget, the less there will be for State and local governmental budgets. If this plan is carried too far, it would practically destroy local self-government. It behooves us, therefore, to give careful consideration to governmental trends in these directions and interpret them not only in their relation to health activities but also to the development and protection of our democratic ideals.

Among the fields of health activities, that pertaining to maternity and infancy has great appeal, as there is not only an intelligent but also a sentimental interest, and often the emotions dominate the intelligence not only of individuals but also of the masses.

The Children's Bureau of the Department of Labor is a good example of the trend of the Federal Government in its health legislation and administration. Its activities, furthermore, have been more or less within the domain of health of mothers, infants, and children. In studying trends one can gain rather exact and pertinent information from studying the records which are to be found in the Annual Reports of the Secretary of Labor.

Originally approved by Congress on April 9, 1912, the Children's Bureau was in the Department of Commerce and Labor with Julia Lathrop as Chief. It was transferred to the Department of Labor upon its creation on March 4, 1913. This Bureau has had a life span of thirty-three years with three chiefs, Grace Abbott and Katharine Lenroot following Julia Lathrop. The original expressed purposes of the Department were "to foster, promote and develop the welfare of the wage earners of the U. S. A. and improve their working conditions and to advance their opportunities for profitable employment."

The stated purposes of the Bureau were to "investigate and report upon—all matters pertaining to the welfare of children, child life among all classes of our people, and shall especially investigate the question of infant mortality, the birth rate, orphanage, juvenile courts, desertion, dangerous occupations, accidents and diseases of children, employment legislation affecting children in the several States and Territories." In the first report it is stated that four bulletins were published, viz., on birth registration, urban baby saving campaigns, prenatal care, and statistical report on the number, age, sex, etc., of children. At this time the staff consisted of 15 persons, and the budget was \$25,640 with \$4,000 as a contingent fund.

The following year it was recommended that the staff be increased to 76 and the appropriation to \$164,640. There were studies on infant mortality and the problem of mothers' pensions received attention. There were in addition other studies which had no bearing on maternal welfare. In 1915 a divisional organization was established consisting of (1) statistical, (2) library, (3) industrial, (4) hygiene, and (5) social service divisions.

In 1916 three new approaches for the development of the programs were stated: (1) studies in child welfare in rural areas by field workers; (2) research study of existing data on maternal mortality; (3) nationwide observance of "Baby Week." An increase of staff to 133 persons and an appropriation addition of \$187,520 to make a total of \$352,160 was recommended. The following purposes were stated: (1) continuance of the infant mortality

study; (2) development of rural studies of maternal and child welfare; (3) development of child labor studies.

In 1917 an administrative division was added for the enforcement of the United States Child Labor Act, and Grace Abbott was made the Director. There was a special appropriation for this purpose. As the result of some studies in our own and other countries it was determined that the conservation of infant life was to be accomplished by "public protection of maternity"; the making "promptly and uniformly available, for all mothers and children, in town and country alike, irrespective of income, the services of nurses, doctors, conference centers and hospitals." The "Children's Bureau recommends the adoption in the U. S. A. of a nationwide plan for the public protection of maternity with Federal aid." The suggested program was to include not less than: (1) Public Health nurses, (2) instruction in schools and universities, (3) conference centers, (4) hospital facilities, (5) proper care at childbirth.

In 1918 the report stressed the public protection of infancy and maternity, cited statistics concerning the relation between family income and infant mortality, quoted mortality figures for mothers and infants and the relationship between maternal care and infant mortality, and pointed out the failure to reduce mortality since 1900.

In 1919 a special allocation of \$150,000 was received from the President's Fund, and certain minimal standards for maternal care were set forth. These included:

1. Sufficient available maternity or prenatal centers to provide for all cases not otherwise receiving such care. Certain standards of care were elaborated.
2. Accessory clinics for pregnant women such as dental, venereal, etc.
3. Maternity hospitals or maternity wards in general hospitals sufficient to provide care in all complicated cases and for all women wishing hospital care; free or part payment for obstetric care in every necessitous case at home or in a hospital.
4. All midwives to have adequate training, to be licensed and supervised.
5. Income sufficient to allow the women to remain home during lactation.
6. Education of the public relative to the importance of problems presented by infant and maternal mortality and their solution.

The funds available during that fiscal year had been increased to \$597,160.

In 1920 an appropriation of \$654,260 was requested for the ensuing year. The report called attention to the fact that before the campaigns of the Children's Bureau only eight States had child hygiene or welfare divisions and that now there were 35. An interesting statement is made in this report: "One of the bureau's most important functions in the field of child health is the service it can render in an advisory capacity to these newly created divisions." For the fiscal year ending June 30, 1921, the expenditures of the Children's Bureau were \$238,383.

It was in November, 1921, that the so-called Sheppard-Towner Act became law. During that fiscal year the expenditures, \$236,751, and an additional \$204,638 were transferred to the States. This Act specifically required that there was to be no payment to the mother, and none for buildings or equipment.

In 1923 the report says, "The Children's Bureau created in 1912 for scien-

tific research in the field of child care has had its usefulness greatly extended during the past year by the passage of the Maternity and Infancy Act."

In March, 1922, the appropriation for the purposes of the above Act was \$490,000. Of this, \$12,500, about 2½ per cent, was for administration; \$240,000 was to be equally divided among the States; and the remainder, \$237,500, was to be apportioned according to population and matched.

Quoting from the report of that year one finds interesting sentences:

"The specific measures involved in State plans are accurate birth registration, improved milk supplies, State surveys of the medical and nursing facilities for maternal and infant care, and registration and supervision of midwives. Everywhere the plans of work are largely educational to be carried out through actual teaching of mothers by public health nurses." "Any public health measure is largely educational." "This is particularly true of maternal and child hygiene."

In 1923 the constitutionality of the "Act," which had been questioned by Massachusetts, was upheld and forty States had accepted the programs. In 1922, \$477,500 were available to the States, and in 1923, \$1,190,000. The report in 1924 indicates that "during the last year real progress has been made by the States both in developing programs especially adapted to local needs and in extending the educational work to a larger number of mothers."

In the report of 1925, the Children's Bureau expended \$342,873, and the funds available for 43 States and Hawaii amounted to \$477,500 available from 1922, and \$1,190,000 for the fiscal year 1923-1924. The specific objectives mentioned were "better care through the teaching of mothers and their education relative to the need and value of skilled supervision during pregnancy, child birth and the lying-in period and more widespread medical and nursing facilities so that adequate maternity and infancy supervision will be available to all who need it."

In 1926 the *Standards of Prenatal Care* were published, and by 1927 two additional States had accepted the provisions of the Act leaving Massachusetts, Connecticut and Illinois as the only exceptions. The five-year appropriation of \$1,240,000 annually ended on June 30, 1927, but special legislation extended it for two years, i.e., until June 30, 1929. The annual report argues that "Any unprejudiced examination of the work done under the Act would show the value of cooperation of Federal, State, and Local Governments in developing better home care for mothers and babies and better community provision for hospital care at the time of child birth." The expenditures of the Children's Bureau were \$337,878, not including the allotments to States.

In 1928 the funds available for the States were \$1,201,725 and the expenditures of the Children's Bureau were \$317,339. The following quotations are pertinent. "In the 16 years that it has functioned as a fact-gathering bureau, public and private agencies interested in the care of children and individual parents have increasingly made use of the information that has been painstakingly and dispassionately assembled by the scientific staff of the bureau."

It is noted in the 1929 report that "The Sheppard-Towner Act, which was approved Nov. 23, 1921, provided for Federal and State co-operation in promoting the welfare and hygiene of maternity and infancy for a five year period. This was later extended for another two years and by 1929, 45 States and the Territory of Hawaii were co-operating with the Children's Bureau

under the Act. It was the obvious intent of Congress in enacting the law that the Federal Government should lead the way in providing for the better care of mothers and children of the nation and to that end it made generous appropriations from the Federal Treasury for use in the States which made like appropriations for the same purpose." "Although Federal Funds are no longer available for actual participation it is the purpose that the Children's Bureau shall continue its recognized leadership in the maternity and infancy work in collecting and publishing helpful information as well as in an advisory capacity." The expenditures were \$316,274.

The report of 1930 indicates the conclusion of the field work on the maternal mortality study begun in 1926 in 15 States. Also progress in the study of the causes of stillbirths and neonatal deaths. Important steps were taken in July, 1929, in planning the work of the Hoover "White House Conference on Child Health and Protection" which was financed by other than government funds. This conference had an important Subcommittee on Prenatal and Maternal Care as part of the Section I Medical Service which held its final sessions in February, 1931. As a result, *The Children's Charter* was promulgated, from which the following excerpt is taken: "The right to grow up in a family with an adequate standard of living and the security of a stable income as the surest safeguard against social handicaps."

The reports of 1931, 1932, 1933, and 1934 show expenditures of \$338,865, \$386,632, \$359,183, and \$343,241, respectively. The *Maternal Mortality Report* was published in 1933, and in 1934 emphasis was placed upon the great need for Federal cooperation with the States along the lines of the previous Maternity and Infancy Act.

The expenditures in 1935 were \$342,631. The report of that year points out that with the "enactment of the Social Security Act of August 14, 1935, and the appropriation of funds to make it operative Feb. 11, 1936, a far-reaching specialized undertaking to safeguard the health and welfare of America's children was inaugurated."

The 1937 report shows the expenditure of \$6,704,024, of which the allocation to States was \$213,176 in 1936, and \$2,788,608 in 1937 for carrying out the maternity and infancy program and a comparable but somewhat smaller amount for the care of crippled children. Quoting, we find that "evidence is steadily accumulating that a direct and courageous attack must be made on the central problem of reducing maternal mortality and morbidity and deaths of infants under one month by extending adequate medical and nursing care to all mothers and infants at the time of delivery and by continuing medical and nursing supervision throughout the prenatal and postnatal periods." At this time the appropriation under the Social Security Act was:

Maternity and Infant Health Service	\$2,820,000
Crippled Children	2,150,000
Child Welfare	1,200,000
Federal Administration	299,000

The report of 1938 indicates a total appropriation of \$8,352,359.

In July, 1938, the National Health Conference's "recommendations in the

fields of maternal and child health called for a gradually expanding program reaching at least by its tenth year a total additional expenditure of \$165,000,000 distributed as follows:

Maternity Care and Care of Newborn Infants	\$95,000,000
Medical Care of Infants	60,000,000
Services for Crippled Children	10,000,000

The Federal Government was to meet approximately one-half by the Social Security Act Appropriation.

In this annual report these appropriations are listed as:

Maternity and Infancy	\$3,700,000
Crippled Children	2,800,000
Child Welfare	1,475,000
Administration	306,000

The annual reports of 1939, 1940, and 1941 indicate expenditures for the respective years of \$8,964,927, \$10,618,693, and \$11,935,944, and in 1942 emphasis is placed upon "the need for public provision for maternity care for wives of men in the armed services and medical care for their children."

During that year the payments to the States were:

Maternity and Infancy	\$5,983,318
Crippled Children	4,053,292
Child Welfare	1,569,009

The 1943 report shows the following expenditures:

Maternity and Infancy	\$5,740,218
EMIC*	1,200,000
Crippled Children	3,862,531
Child Welfare	1,582,774

In 1944 the report indicated payments to the States as follows:

Maternity and Infancy	\$ 5,946,183
EMIC	29,700,000
Crippled Children	3,781,751
Child Welfare	1,423,314

"This new program has contributed to the development of improved standards of maternal and infant care and has stimulated widespread interest in developing additional resources for medical, hospital and nursing care."

There is now before Congress a bill entitled Maternal and Child Welfare Act of 1945. Under Title I, its purposes are enumerated as follows:

1. Maternity care, including medical, nursing, dental, hospital, and related services.
2. Preventive maternal and child health work, including mental health.
3. School health services.
4. Diagnostic services and care of sick children, including medical, nursing, hospital, and related services.
5. Dental care of children.
6. Correction of defects and conditions likely to interfere with normal growth and development and the educational progress of children.
7. Demonstration projects in the field of maternal and child health.
8. Training of professional and technical personnel.

*The Emergency Maternity and Infant Care appropriation was \$4,400,000.

The appropriation of \$50,000,000 is authorized for the fiscal year ending June 30, 1946.

Under Title II, \$25,000,000 is appropriated for the care of crippled children.

Under Title III, there is an appropriation of \$20,000,000 for child welfare. The approval of all State plans are vested in the Chief of the Children's Bureau. All plans are to be in accord with Title V of the Social Security Act. "To carry out these functions and to administer the programs provided for under this act, \$5,000,000 is authorized for appropriation to the Children's Bureau."

In a paper published in the *AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY*, January, 1945, page 128, Daily probably expressed the views of the Children's Bureau in advocating hospital care by specialists for all maternity cases. The number of specialists requisite is estimated at 10,000, the annual compensation to vary from \$2,000 to \$20,000. The necessary hospitals could be built and equipped over a period of ten years at an annual expenditure of \$15,000,000.

The estimated cost of providing medical and hospital care for all maternity patients would be about \$250,000,000 yearly or about \$100 for each birth.

The EMIC program, which reached a peak load of some 20 to 25 per cent of all deliveries, should give some idea of the amount paid by the Federal Government for medical and hospital care for these maternity patients and their babies, but it is to be doubted that this is an accurate index of the actual cost, and it is seriously questioned whether or not it would prove to be satisfactory compensation for the type of service which should be had. Under this plan the government has made payments to the individual doctors and hospitals, usually on a flat fee basis and a per diem cost plan. While the family has been relieved of financial burden and responsibility it is to be seriously doubted whether or not the quality of care has been improved.

The main theme of this paper has been to show governmental trends by documentary evidence. The Children's Bureau has been the Federal agency which has been interested in the welfare and health of children and women. The quoted evidence shows that the original concept was not that which now constitutes its major activity, namely, a "Health Agency." Its activities have changed from investigation, advising, and administration, to supervision, administration, and service. It is now concerned with women as well as infants and mothers. Under the now proposed act of 1945, all individuals under 21 years of age come under its domain. Primarily the programs have to do with health as distinguished from welfare.

If one considers the scope of the proposed act, the only portion of our population not included within its provisions would seem to be that relatively small proportion of males who are over 21 years of age.

Health is not acquired in or limited to any one sex or age period or to any physiologic or anatomic state. Health is something that is positive and not merely negative. As applied to individuals and communities it is the result of carefully integrated comprehensive knowledge intelligently applied.

The application begins with the individual and extends up through the family and the community to include progressively larger units of government, and with present trends no one nation can be a law unto itself. There must be one unified health agency based upon local units of varying size and extending upward to one Federal health agency. At present there would seem to be two major Federal health agencies developing: one in the Children's Bureau and the other in the United States Public Health Service, with budgets amounting to millions of dollars yearly. There are also other Federal departments which have major health activities which are related to their principal functions. The growth of these Federal health agencies with increase in personnel and appropriations has been rapid and phenomenal, and one wonders how much of the national income can be absorbed by the Federal government without seriously curtailing the amount of money available to the local communities for taxation to support their health and educational activities. How much of the national income can be diverted to Washington to be redistributed to the various communities from which it came without eventually limiting this taxing ability of the States and local communities? These are matters for the economists to discuss and perhaps decide, but we as citizens and doctors are seriously concerned about these trends in the functions of Federal bureaus and departments.

There is much in the reports to indicate that the Children's Bureau assumes credit for progress in the field of maternity and infancy and, while without doubt the Bureau has contributed much, it must be remembered that medical sciences have progressed independently and that the advice of medical experts familiar with these advances have been gratuitously available to the Bureau.

These experts in their various fields have been the leaders, and the Bureau has been the medium. The point which should be stressed is that these men of science have been the product of the American system of medical education, investigation, and practice. America has now advanced to world leadership in the medical sciences, and the major issue is flatly before us and the citizens of our country. Should present governmental trends be permitted to change seriously, by legislative act, an educational, research, and service system of medical care which has stood the test of time, of war, of pestilence, and of peace, and which is still progressing on all fronts? Should not the present program be evolved and not be submitted to revolutionary hothouse development? Should it not be developed upon a basis fundamental to our form of democracy and in accord with the dignity of the individual citizen and of a worthy profession?

Let it not be forgotten that the quality of medical service depends upon the quality as well as the quantity of those who render it. The medical profession must be progressively maintained both qualitatively and quantitatively.

Lastly, the rendering of high quality medical care depends not only upon personnel but also upon adequate facilities, which have never been available in all areas through no fault of the medical profession.

Let the cooperative efforts of Federal, State, and local resources provide the facilities, and private professional enterprise develop the personnel.

THE RH FACTOR IN OBSTETRICS*

H. F. TRAUT, M.D., B. C. McIVOR, PH.D., J. HOWARD, A.B., S. P. LUCIA, M.D.,†
AND L. CHARVET, M.D., SAN FRANCISCO, CALIF.

(From the Department of Obstetrics and Gynecology and the Department of Preventive Medicine of the University of California Medical School)

SELDOM has a medical discovery been accorded practical application as widely and intelligently as that which has followed the announcement of the Rhesus blood factor by Landsteiner and Wiener in 1940. In four years' time, not only has its implications in blood transfusion been taken into account, but a great deal has been learned concerning the various complications it imposes in the obstetric field. All this activity is in sharp contrast to the more important announcement of the A and B blood factors by Landsteiner in 1901, after which a considerable number of years elapsed before blood grouping and blood matching became well understood or widely used by the medical profession. The difference in reaction may be taken as a measure of the importance that blood transfusion and hematology in general have assumed in medical practice.

Although the Rh factor is important to all who use blood as a therapeutic agent, it is particularly in the field of obstetrics that this discovery has its greatest significance, because not only is the obstetrician concerned with untoward transfusion reactions, but also he must take into account the fact that the transfusion of an Rh-negative patient with Rh-positive blood, on the one hand, or the harboring in utero of an infant which has inherited Rh-positive blood characteristics from an Rh-father, on the other, may induce the production of antibodies which may and often do affect the offspring adversely. In fact, this process may seriously modify the reproductive period of as many as 15 to 18 per cent of women in the childbearing period of life.

It is well for us, therefore, to understand in so far as is possible the various elements of the problem which this characteristic of the red blood cell imposes upon us.

Historical Background

Although rapid progress has followed Landsteiner and Wiener's announcement in 1940, actually the sequence of events leading up to that enunciation occupied a considerable period of time. As long ago as 1905 Dienst noted that a remarkably high postpartum titer of agglutinins in maternal blood serum occurred when the mother's blood contained an A or B agglutinin which was capable of agglutinating the red blood corpuscles of her offspring. He believed that this resulted from an antigenic action of fetal blood cells

*Read before the Academy of Medicine, Portland, Oregon, Jan. 10, 1945.

†Assisted by a grant from the Columbia Foundation.

which had somehow gained access to the maternal circulation. Others, Murray in 1910, McQuarrie in 1923, Ottenberg in 1923, Gruhitz in 1924, and Allen in 1926, pondered the concept of fetal and maternal incompatibility in trying to explain eclamptic toxemia with various resulting opinions. It was not until 1938 when Darrow approached the matter from the point of view of the incidence of erythroblastosis that anything like our present hypothesis was forthcoming. She suggested that there was a fundamental difference in the chemical constituents of fetal and maternal blood of such a kind that a maternal reaction to the fetal type occurred and was followed by transmission of the resulting maternal antibodies through the placenta, bringing about agglutination of fetal cells and subsequently the syndrome known as erythroblastosis fetalis. Her hypothesis lacked confirmation.

Meanwhile, a parallel group of observations concerned primarily with transfusion reactions had stimulated a trend of thought which also led to conclusions somewhere near the truth as we now understand it. Stetson, in 1933, reported the history of a young woman who, after five successful pregnancies, then had serious transfusion reactions during a series of blood transfusions when the husband was the donor, meanwhile tolerating the blood of brothers as donors with no reaction. He postulated that an inherited isoagglutinin must be present in the members of the patient's own family and that the transfusion of foreign blood (husband) probably stimulated the production of agglutinins such that it caused reactions to the bloods of all persons outside her family.

Culbertson and Ratcliffe, Parr and Krischner, Goldring and Graef were others who reported transfusion reactions under circumstances which suggested that "intragroup" transfusion reactions were due to antibodies induced by transfusion or produced by a pregnancy.

It was not until 1939, however, that Levine and Stetson reported an irregular isoagglutination reaction in which a pregnant woman agglutinated 80 per cent of the blood of donors of the same blood grouping, and inferred that she had become immunized to some factors which had been inherited by the fetus from its male parent.

It became quite probable, therefore, that when atypical agglutinins were present, producing a transfusion reaction, several other factors were also true: either the patient had had previous transfusions or had been recently pregnant, or that the blood cells of the immediate family, exclusive of the husband, were the only ones which the patient's serum did not agglutinate. On the other hand, it was shown that the husband's blood was most likely to cause a severe transfusion reaction. Furthermore, the possibility had been suggested of fetal inheritance of paternal antigens, which were absent in the mother, resulting in the production of maternal antibodies of such a titer that a reaction followed transfusion from many donors.

In 1940 Landsteiner and Wiener demonstrated an agglutinin in the blood of the Rhesus monkey. After injecting monkey blood into rabbits, the serum of the latter contained agglutinins capable of reacting with a high per-

centage of human red blood cells. They designated these agglutinogens as "the Rh factor" because it was found to be a constant characteristic of the red blood cells of the Rhesus monkey. Those human cells which were not agglutinated by the antirhesus serum were designated as Rh negative, whereas those which were agglutinated by it were called Rh positive.

Wiener and Peters, in 1940, made the first practical application of the Rh immunizing principle when they demonstrated that three Rh-negative persons having transfusion reactions following the use of homologous bloods probably had been transfused and sensitized previously with Rh-positive blood.

In the same year Levine demonstrated that a number of women who had had repeated abortions possessed blood sera in which isoagglutinins similar to the Rh factor were present. Following this lead, Levine and his co-workers investigated a number of women who had given birth to erythroblastotic infants and discovered that most of the mothers were Rh negative and, furthermore, that the incidence of Rh negativity in this group was many times that found in the general population. This led to the hypothesis that erythroblastosis fetalis is the result of the formation of Rh agglutinins on the part of the Rh-negative mother either as the result of transfusions of Rh-positive blood or the harboring of an Rh-positive fetus. In the latter instance, they postulated transmission of fetal red cells into the maternal circulation (due to an imperfect placental barrier) with the resulting formation of agglutinins which then retraversed the placenta and produced agglutination and probably hemolysis of the fetal red blood cells.

Thus has grown our present concept of the operation of the Rh factor in transfusion and in pregnancy.

Incidence of Rh Factor in the General Public

As a result of the investigations of numerous workers, the incidence of Rh positivity and Rh negativity in various parts of the world has become known. Altogether more than twelve thousand individuals have been tested, with results showing about 85 per cent to be Rh positive and about 15 per cent Rh negative. Table I, from Potter, gives the sources of this information. It has been found that there are racial differences in these characteristics.

TABLE I. RACIAL DIFFERENCES IN REACTION TO STANDARD ANTI-RH SERUM OF THE TYPE AGGLUTINATING THE CELLS OF 85 PER CENT OF WHITE PERSONS (FROM POTTER)

AUTHOR	RACE	TOTAL NUMBER OF SUBJECTS	REACTION TO ANTI-RH SERUM			
			POSITIVE		NEGATIVE	
			NO.	%	NO.	%
Combined data	White	7,620	6,485	85.1	1,135	14.9
Landsteiner and Wiener	Negro	113	104	92.0*	9	8.0*
Levine	Negro	264	252*	95.5	12*	4.5
Landsteiner, Wiener and Matson	American Indian					
	Full blooded	120	119	99.2	1	0.8
	Mixed blooded	155	148	95.5*	7	4.5*
Levine and Wong	Chinese	150	149	99.3	1	0.7

*Figures calculated from author's percentages.

Whereas the white race is approximately 85 per cent Rh positive, the Negro is about 93 per cent, and the Indian and Chinese from 95 to 99 per cent Rh positive.

In our own experience (Table II) in analyzing 1,479 blood specimens we have found 82.4 per cent to be Rh positive, and 17.6 per cent to be Rh negative. The relationships to the other blood factors are shown.

Inheritance of the Rh-positive characteristic is of considerable importance, therefore, particularly in white populations. It has been found that it is inherited as a dominant in the Mendelian manner. Landsteiner and Weiner have found that inheritance is brought about by two allelic genes which they have represented as Rh (positive) and rh (negative). The phenotype Rh positive would embrace genotypes Rh Rh (homozygous) and Rh rh (heterozygous), while the phenotype Rh negative would include only rh rh inheritance.

II
TOTAL NUMBER OF
BLOOD SPECIMENS ANALYSED AS OF 6-30-44
PERCENTAGE DISTRIBUTION

GROUP	Rh+	Rh-
AB	30	31
A ₂ B		
A	41.7	40.6
A ₂		
B	11.2	10.3
O	44.2	46.0

TOTAL NO: 1479
% Rh+ : 82.4
% Rh- : 17.6

II₁
INHERITANCE OF THE RH FACTOR
Material obtained from study of 60 Rh negative women
from U.C.H. Obstetrical Department.

		FATHER	
		Rh negative 15%	Rh positive 85%
CHILD	Rh negative 40%	9 = 100%	15 = 29% ∴ heterozygous
	Rh positive 60%	0	36 = 71%

The accompanying table (II₁) indicates the inheritance as disclosed by our study of sixty Rh-negative women, their husbands, and the resulting offspring. Forty per cent of the offspring were Rh negative and 60 per cent were Rh positive. Of the Rh-negative matings, 100 per cent were Rh negative, which might be expected. However, of the matings of Rh-positive husband and Rh-negative wife, 29 per cent of the offspring were Rh negative, which can only be interpreted by postulating that some of the husbands were heterozygous. The remaining 71 per cent were Rh positive, the result of homozygous parentage or the inheritance of the dominant Rh (plus) gene from a heterozygous parent.

However, the matter of Rh phenotypes does not appear to be as simple as this formula might imply, for it has been discovered that there are several groups and subgroupings of Rh-positive phenotypes, eight in all, as the accompanying table (III) from Wiener, Sonn, and Belkin will indicate, and with these as phenotypes at least twenty-one genotypes are theoretically possible. It is, therefore, obvious that there are many possible types of Rh positivity, the meaning of which in terms of transfusion and reproductive compatibility remain to be studied. Indeed, we may conclude that the full importance of the relationships of Rh-positive and Rh-negative blood characteristics must be the subject of extensive and prolonged study before any exact formula can be framed as to their ultimate significance.

TABLE III. THE RH BLOOD TYPES AND THEIR THEORETIC GENOTYPES
(FROM WIENER, SONN, AND BELKIN)

PHENO- TYPE	REACTIONS WITH Rh ANTISERUMS					APPROXI- MATE FRE- QUENCY IN WHITE PERSONS (NEW YORK CITY)	THEORETI- CALLY POSSIBLE
	ANTI-Rh	ANTI-Rh ₁	ANTI-Rh ₂	ANTI-Rh'	ANTI-Rh''	%	
Rh	-	-	-	-	-	12.75	rhrh
Rh ₁	+	+	-	+	±	50	{ Rh ₁ Rh ₁ Rh ₁ rh Rh ₁ Rh Rh ₁ Rh' Rh'Rh
Rh ₂	+	-	+	+	+	15.5	{ Rh ₂ Rh ₂ Rh ₂ rh Rh ₂ Rh Rh ₂ Rh'' Rh''Rh
Rh ₁ Rh ₂	-	+	+	+	+	17	{ Rh ₁ Rh ₂ Rh ₁ Rh'' Rh'Rh ₂
Rh	+	-	-	+	-	2.5	{ RhRh Rhrh
Rh'	-	+	-	+	-	2	{ Rh'Rh' Rh'rh
Rh''	-	-	+	-	+	0.25	{ Rh''Rh'' Rh''rh
Rh'Rh''*	-	+	+	+	+	----	Rh'Rh''

*This theoretically possible type has not yet been encountered, which is not surprising considering the extremely low value of the calculated frequency of the genotype Rh'Rh''.

Modes of Development of Antibodies in Response to Rh Antigens

The Rh substance appears to be on the surface or within the body of the erythrocytes of about 85 per cent of the general populace. It is also probably present in the cells of the liver, spleen, kidney, and salivary glands as well as in the general body fluids. This characteristic develops early in life, a matter of great importance in obstetrics; in fact, it has been demonstrated as early as the twelfth week of life. Antigenic potency fluctuates greatly as might be

suspected from the possible variations in inheritance of the different Rh subgroups. This fact may explain why some transfusions, with bloods incompatible as far as the presence or absence of the Rh factors are concerned, have been devoid of appreciable reaction. On the other hand, it may also explain why some Rh-negative women repeatedly harbor Rh-positive infants without serious reactions toward the fetus.

Rh agglutinins are not normally found in the human body and must either be transmitted passively by transfusion or be generated actively as a result of transfusion or pregnancy. The response on the part of the host depends upon the antigenic potency of the red blood cells introduced into the circulation as well as the ability of the recipient to produce immune bodies. Thus, some red blood cells are low in antigenic quality on the one hand and some individuals are latent reactors on the other. Whereas, the reverse and all gradations between may be true, giving rise to a wide variety of response.

In general, however, it may be said that the evidence thus far accumulated goes to show that the intimate relationship of mother and fetus in pregnancy provides a much more favorable background for the development of Rh antibodies than does transfusion alone.

It is of interest, therefore, to ascertain if possible how it may be that fetal red blood cells enter into the circulation of the mother and thus make this reaction possible. It has been known for many years that many women who die during pregnancy show at autopsy significant groups of placental cells and even placental villi which have been transported by the blood stream into the pulmonary vascular tree. This has been termed deportation of villi. It would be easy, therefore, to imagine that such breaking off of villus structures might be accompanied by a considerable number of fetal red blood cells. This may be one process whereby the intermixture of blood cells occurs. Another process, and one about which we have recent information, is the formation of hematomas about the tips of placental villi in the intervillous spaces of the placenta. Traut and Javert found several instances in which such hematomas contained nucleated red blood cells, suggesting the possibility that, due to degenerative changes in the syncytium of the placenta, such a fetal hemorrhage had occurred in the placentas of obviously erythroblastotic infants. We have no knowledge as to how frequently this may occur in so-called normal pregnancies. If it does occur, the difference in maternal reaction may be accounted for on the basis that the Rh characteristics may become well defined in the infant before that of the A and B factors.

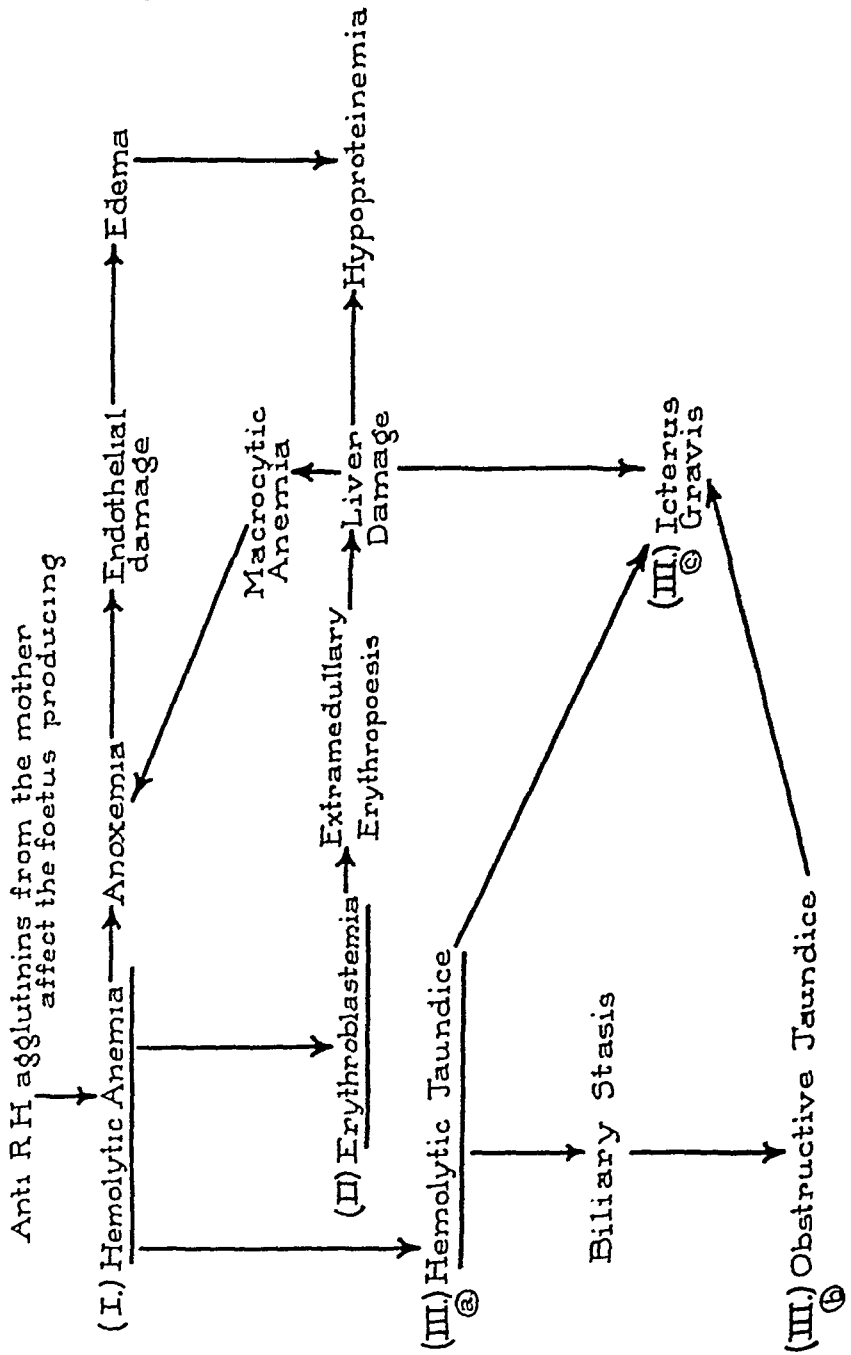
Whatever the mechanism may be for providing an intermixture of maternal fetal blood elements, experience has shown that the Rh-negative mother who carries an Rh-positive infant will frequently, and more often after the first pregnancy, develop Rh antibodies which she then may transmit to her progeny by way of the placenta.

The effect upon the fetus depends upon many factors some of which we do not fully comprehend.

TABLE IV

SUGGESTED PATHOGENESIS OF ERYTHROBLASTOSIS FOETALIS

(After Davidsohn)



Hemolytic Diseases and Erythroblastosis Fetalis

Curiously enough, the action of Rh antibodies in vitro results in agglutination, whereas, in vivo, the response is not only agglutination but the more extreme process of actual red blood cell destruction, namely hemolysis. The accompanying diagram, Table IV, after Davidsohn, may serve to explain the effect of this reaction upon the fetus. It is a pathologic speculation that there are two general types of reactions, red blood corpuscle destruction with its sequelae on the one hand, and hydrops on the other. That they may be inter-related and interdependent the diagram will show; however, one cannot accept this explanation except tentatively without more convincing evidence as to the relationship of hypoproteinemia and Rh agglutinins.

Erythroblastosis is an ill-chosen term, indicating as it does only one criterion of disease which may be common to a number of pathologic conditions of the newborn infant. It might be better to speak of hemolytic anemia of the newborn infant. Erythroblastosis must be differentiated from physiologic jaundice, prematurity, intracranial hemorrhage, hemorrhagic disease, congenital heart disease, congenital syphilis, sepsis neonatorum, familial acholuric jaundice, Winkel's disease, and hypoproteinemia. Despite this rather lengthy list of diseases similar at least in some respects to the typical case of erythroblastosis, the latter is not difficult to recognize. The jaundice due to hemolysis, the enlargement of the spleen and liver associated with its dysfunction, as well as the blood picture showing an abnormal number of the early red blood cells is pathognomonic. Occasionally, instead of icterus, one finds with the above, extensive and massive edema of the fetus, the umbilical cord, and the placenta. Indeed, icterus gravis would seem to be one mode of termination of the disease syndrome and fetal hydrops another. Thus far we seem to be unable to differentiate them etiologically and feel that they are alternate expressions of the effect of the Rh antibodies upon the tissues of the fetus.

Undoubtedly, in addition to these well-defined clinical pictures there are many of lesser degree, some of them barely recognizable from the normal. It may be that the so-called physiologic jaundice of the newborn infant will eventually be found to be an expression of some blood dyscrasia, if not due to the Rh group, then to that of some other as yet unrecognized immunologic mechanism. Careful study of the subclinical varieties of the disease may be most helpful in developing our knowledge of its pathogenesis and treatment. To deny their existence is but to question biologic variation. We must expect to find all gradations.

In our experience it would seem probable that there are a number of sub-clinical evidences of hemolytic disease of the newborn infant, associated or not with Rh-negative inheritance, which should receive careful scrutiny in this connection. Such conditions as enlarged liver, enlarged spleen, nucleated red blood cells in excess of 5 per 100 white cells, jaundice, bleeding tendencies, anemias, hydrocephalus, and spontaneous miscarriage or abortion may or may not be related to the subject under consideration. They have seemed at times to have an increased incidence in matings involving mixed Rh factors.

TABLE V

RELATIONSHIP BETWEEN Rh NEGATIVE MOTHERS AND HEMOLYTIC DISEASE OF THE NEWBORN

MATERIAL FROM UCH OBSTETRICAL DEPARTMENT - 10-13-43 - 12-31-44

Rh CHARACTER OF MOTHER FATHER CHILD		CONDITION OF CHILD
11ORh	53Rh+	35Rh+ <ul style="list-style-type: none"> 27 NORMAL 4 SUBCLINICAL MANIFESTATION 4 ERYTHROBLASTOSIS FETALIS (1?)
	15Rh-	14 NORMAL <ul style="list-style-type: none"> 1 SUBCLINICAL MANIFESTATION
	3Rh(?)	1 NORMAL <ul style="list-style-type: none"> 2 SUBCLINICAL MANIFESTATION
	0Rh-	7 NORMAL <ul style="list-style-type: none"> 1 SUBCLINICAL MANIFESTATION - Enlarged spleen
49Rh	31Rh+	23 NORMAL <ul style="list-style-type: none"> 5 SUBCLINICAL MANIFESTATION 3 ERYTHROBLASTOSIS FOETALIS (1?)
	14Rh-	13 NORMAL <ul style="list-style-type: none"> 1 SUBCLINICAL MANIFESTATION - Enlarged liver, nucleated red blood cells
	4Rh(?)	3 NORMAL <ul style="list-style-type: none"> 1 SUBCLINICAL MANIFESTATION - Spontaneous abortion

CASE
 1 Enlarged liver, spleen, nucleated red blood cells
 2 Enlarged spleen
 3 Enlarged liver and spleen
 4 ERYTHROBLASTOSIS FETALIS (1?)

Premature
 Enlarged spleen
 Nucleated red blood cells
 Enlarged spleen, nucleated red blood cells
 Spontaneous abortion

CASES
 1 Premature - died
 2 Enlarged liver
 3 Enlarged liver, subconjunctival hemorrhage
 4 Enlarged spleen
 5 ERYTHROBLASTOSIS FOETALIS (1?)

Unquestionably many of the Rh-positive fetuses conceived by Rh-negative mothers do not survive to develop the recognizable features of hemolytic disease of the newborn infant. Instead, they succumb early in fetal life, in the first or second trimester. For this reason the parentage of all abortions should be carefully studied with regard to the Rhesus factor.

Relationship of Rh Negativity to the Incidence of Hemolytic Disease of the Newborn Infant (Erythroblastosis) and Subclinical Disturbances

In a group of 110 Rh-negative mothers whose bloods and that of their offspring have been studied (Table V) 66 Rh-positive infants were born. Of this group, erythroblastosis was diagnosed seven times, giving an incidence of 10.6 per cent. If our hypothesis as to the etiology of erythroblastosis is correct, one might expect a higher incidence of the disease. However, there are a number of conditions which may explain the disparity between the potential and the actual incidence. The quality of the placental barrier may be of a better sort in some pregnancies than in others; the maternal reaction to the Rh antigen may be variable; and finally, the antigen of the fetal blood cells themselves may be of different potentialities. Such possibilities make the study of the titers of Rh antibodies in the maternal blood of great importance.

In addition to the frankly erythroblastotic infants there were nine infants with definite abnormalities such as to suggest that the abnormalities may have been lesser expressions (subclinical) of the disease, thus making an incidence of abnormality for this subgroup of 14.8 per cent. If we wish to add the total incidence of abnormality for the whole group, we arrive at 24 per cent.

It is of interest to note also that there were three instances of subclinical abnormality such as we have spoken of in Rh-negative infants born to Rh-negative mothers. One of these mothers had a 4-plus anti-Rh titer throughout her pregnancy, which may have been engendered by previous pregnancies or by transfusion. The other two mothers may have been sensitized in a similar manner, but, unfortunately, we do not have the data which would enable us to make a definite statement.

Relationship of Anti-Rh Titer to the Incidence of Fetal Pathology

For some time we have been determining the titer of the Rh antibodies in our Rh-negative mothers and have expressed this as 1 plus, 2 plus, up to 4 plus. Unfortunately, the complete data upon this material and its relationship to the duration of pregnancy, together with the incidence of fetal pathology, is not yet available. However, a preliminary statement can be made at this time.

Of 21 Rh-negative women showing definite anti-Rh titers ante partum, the children of nine of them (43 per cent) showed some abnormality, four of which were frankly erythroblastotic, one was questionably so, and four showed subclinical manifestations such as prematurity, enlarged spleen, nucleated red blood cells, enlarged liver, and hydrocephalus.

There was an interesting group of 8 Rh-negative mothers who showed anti-Rh titers post partum only. In the offspring of these, two, or 25 per cent, had erythroblastosis and two more were questionable erythroblastotics. A high

incidence of abnormality, indeed. One cannot but wonder why the titer appeared only after delivery. Did the fetus so effectively absorb the antibodies as to make antepartum demonstration of them in the maternal blood impossible? Or did fetal blood become more available to the maternal circulation during the process of parturition? At this stage we can only speculate as to the real cause.

On the other hand, 37 Rh-negative mothers, showing no appreciable anti-Rh titer either during pregnancy or afterwards, produced infants on five occasions which had some of the subclinical manifestations. There were no instances of frank erythroblastosis in this group.

The study of titers is, therefore, only suggestive in the sense that the intensity and the timing of the maternal reaction may bear some relation to the effect of the antibodies upon her offspring.

Observations Upon Rh-Positive Mothers Married to Rh-Negative Husbands

The frequency of the relationship of Rh-negative fathers and Rh-positive mothers is one of the unknowns in this field and will remain so until it is possible to determine the pedigree of *all* marital relationships. We do know, however, that this relationship may be associated with fetal inheritance, bringing into play agglutinogens to which the mothers react in a manner deleterious to the offspring. We have encountered one instance of erythroblastosis and five instances of subclinical abnormality, one of the latter being a case of Kernicterus.

Treatment of Newborn Infants Having Hemolytic Disease

The first requirement is to be forewarned. To accomplish this we may sometime decide to pedigree all bloods of married couples. Certainly this is as important to the welfare of society as the legally required Wassermann reaction for syphilis. At least we can say that all women who have had transfusion reactions and all secundigravida and all women having had repeated abortions or fetal anomalies of a suggestive nature should be investigated, and, if found Rh negative, then their husbands should be accorded the same study.

As many of the offspring who succumb to hemolytic disease do so during the last few weeks of pregnancy, it has been suggested that pregnancies might be terminated before the end of the tenth lunar month. It is doubtful whether this would be of any avail as more infants die neonatally of this disease than are stillborn and, in addition, one would have the added handicap of prematurity with which to cope.

Certainly the avoidance of any means of analgesia or anesthesia which is associated with a decreased oxygen-carrying capacity on the part of the maternal blood should be practiced during labor or delivery.

It may be, however, that when we learn more about the titers developed by mothers, a high level which begins to drop may be an indication of increased rapidity of absorption of the antibodies by the fetus and that interruption of pregnancy at that time would result in a reduced degree of damage to the infant.

At present, the most important feature in the treatment of hemolytic disease of the newborn infant seems to consist in prompt transfusion of the infant with Rh-negative blood from some other donor than the mother. This should be repeated in all probability on several occasions. As a rule, a red blood count of 3,000,000 or less is indication for transfusion, and if 5 per cent or more of the cells are nucleated, then the urgency is increased. If the red blood count be as low as 2,000,000, the chance of survival of the infant is small and all haste should be used to transfuse. Red blood counts done on cord blood as soon as the infant is born should be routine procedure on all infants of Rh-negative mothers. Such a precaution provides the earliest means of recognition of a hemolytic anemia which may have been active in utero. Thereafter, the counts should be repeated at six-hour intervals. Other procedures, such as the administration of vitamin K to check a bleeding tendency, while doing no harm, probably serve no useful purpose because the liver damage causing the bleeding tendency has already occurred and usually the infant does not lack vitamin K. At any rate, vitamin K frequently fails to alleviate the bleeding tendency.

Oxygen therapy has proved to be of some assistance, particularly in the icteric and anemic groups of infants, especially if the red blood count be markedly reduced. The hydropic type of fetus offers the greatest challenge because of the marked hypoproteinemia as well as anemia. The mortality in this group is so high that only the most prompt exercise of the above measures offer any hope for survival.

The Need for Clarification of the Clinical Diagnosis of Erythroblastosis

The diagnosis of the lesser degrees of erythroblastosis offers considerable difficulty because they may closely resemble physiologic jaundice, jaundice due to birth injuries, septicemia, and a variety of anemias of the newborn infant. Clarification will come only as a result of the close cooperation between obstetrician, pediatrician, hematologist, and pathologist. This is all the more important because it is in this group that the greatest hope of salvage lies. The recognition of the possibility of isoimmunization in antenatal obstetric patients will provide the background for prompt and special care on the part of the obstetrician. This, followed by examination of the cord blood at the time of birth, with transfusion if severe anemia or nucleated red blood cells be found in excess of 5 per cent, will add to the life expectancy of the infant. If, in addition, liver or spleen enlargement or icterus be present, the diagnosis becomes clearer and the need for prompt measures is definitely indicated. When survival of the infant is not achieved, careful autopsy studies are of the greatest importance in establishing the cause of death, and in clarifying the clinical impressions which have preceded death.

References

- Darrow, R. R.: *Arch. Path.* 25: 378, 1938.
- Wiener, A. S., and Peters, H. R.: *Ann. Int. Med.* 13: 2306, 1940.
- Levine, P.: *Cincinnati J. Med.* 23: 596, 1943.
- Davidsohn, I.: *M. Clin. North America* 28: 232, 1944.
- Javert, C. T.: *Surg., Gynec. & Obst.* 74: 1, 1942.

- Taylor, G. L., and Race, R. R.: *Brit. M. J.* 1: 288, 1944.
Potter, E. L.: *Am. J. Dis. Child.* 68: 32, 1944.
Dienst, Arthur: *Arch. f. Gynaek.* 65: 369, 1902.
Murray, H. L.: *J. Obst. & Gynaec. Brit. Emp.* 18: 225, 1910.
McQuarrie, I.: *Bull. Johns Hopkins Hosp.* 34: 51, 1923.
Ottenberg, Ruben: *J. A. M. A.* 81: 295, 1923.
Gruhzit, O. M.: *Am. J. Obst. & Gynec.* 7: 588, 1924.
Allen, W. M.: *Bull. Johns Hopkins Hosp.* 38: 217, 1926.
Stetson, R. E.: *S. Clin. North America* 13: 319, 1933.
Culbertson, C. G., and Ratcliffe, A. W.: *Am. J. M. Sc.* 192: 471, 1936.
Parr, L. W., and Krischner, H.: *J. A. M. A.* 98: 47, 1932.
Goldring, W., and Graef, I.: *Arch. Int. Med.* 58: 825, 1936.
Levine, P., and Stetson, R. E.: *J. A. M. A.* 113: 126, 1939.
Landsteiner, K., and Wiener, A. S.: *Proc. Soc. Exper. Biol. & Med.* 43: 223, 1940.
Levine, P.: *Am. J. Clin. Path.* 11: 898, 1941.
Levine, P., and Polayes, S. H.: *Ann. Int. Med.* 14: 1903, 1941.

THE SURGICAL CORRECTION OF CONGENITAL APLASIA OF THE VAGINA

An Evaluation of Operative Procedures, End Result, and Functional Activity of the Transplanted Epithelium

NORMAN F. MILLER, M.D., J. ROBERT WILLSON, M.D.,* AND JAMES COLLINS, M.D.,
ANN ARBOR, MICH.

(From the Department of Obstetrics and Gynecology, University of Michigan)

ALTHOUGH congenital absence of the vagina has been recognized since earliest antiquity, its surgical correction began only a little over a century ago. Since the first reported attempt at surgical correction by Dupuytren¹ in 1817, there have been many hectic years of trial and error, of weighing the psychological evils of the anomaly against the risks of operation. Today, fortunately, all this has changed. There no longer appears to be any valid reason why girls with congenital aplasia of the vagina should not receive the benefit of modern surgical correction, and at a sufficiently early age to minimize psychological trauma. For these young women there are today satisfactory methods of treatment, but this was not always so. Indeed, the cycle through which their wheel of fortune has revolved represents a small, but interesting phase in gynecologic history. Steinmetz² presented an interesting historical review of the subject in 1940.

The incidence of vaginal aplasia is not definitely known, but Engstadt considers one in five thousand births a fair figure. Probably the condition is more common than was formerly believed because some afflicted individuals fail to seek treatment and many treated cases remain unreported. While the condition must have been recognized since earliest times, Burrage² states that the first reported case was described by Realdo Columbus in 1752. By 1895, however, Neugebauer had knowledge of one thousand collected cases.

The condition represents an embryonal or developmental defect and may reveal itself as a partial or complete absence of the vagina. Since the genital and urinary organs have a close embryonic origin, developmental anomalies of adjacent urinary organs may also be encountered. This is an important point to remember since a pelvic mass found in connection with aplasia of the vagina may mean a pelvic kidney. One of our patients had only one kidney (Fig. 1). Counseller and Sluder, Jr.,³ investigated 15 of their patients urologically and found only 6 had normal kidneys. Of the remaining 9, the left kidney was congenitally absent in 6. Two had ectopic pelvic left kidneys and one had a duplication of the left ureter.

Earliest treatment probably included pressure makeshifts of one sort or another. Their use is but dimly recorded and leaves much to the imagination. First attempts at

*Now at the University of Chicago, Department of Obstetrics and Gynecology.

surgical treatment remain sketchy, but, in 1904, James F. Baldwin⁴ described a contemplated operation whereby he hoped to use a loop of terminal ileum or sigmoid colon, carrying it down through a newly dissected channel between the bladder and rectum. Baldwin believed there would be sufficient mesentery to permit such mobilization of the bowel (Fig. 2). He did not, however, have an opportunity to try this technique until 1907. By 1910, he had successfully operated on four patients by this method. Meantime, Mueller⁵ and Mori⁶ each reported a successful case operated by Baldwin's technique, making a total of six cases without mortality.

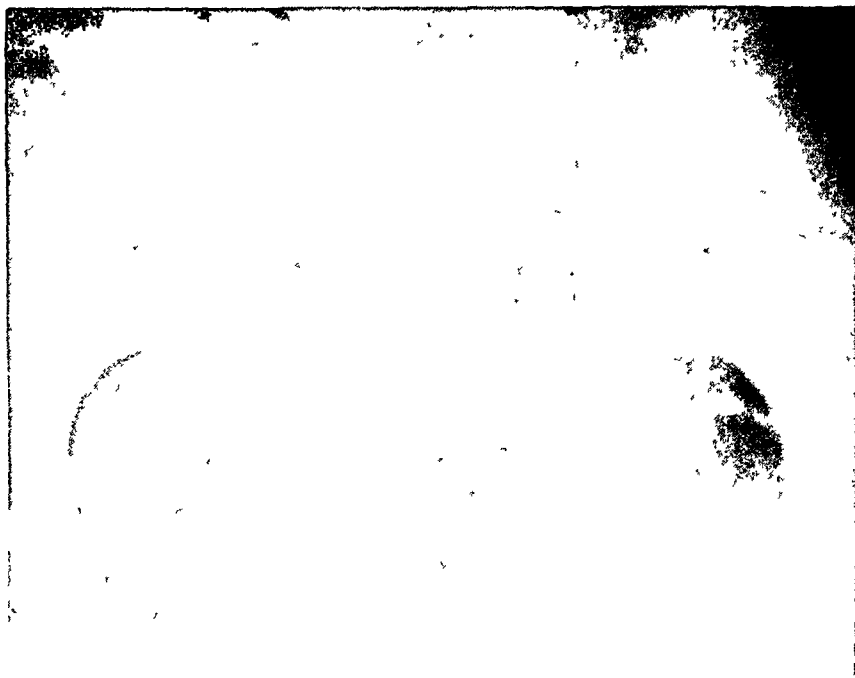


Fig. 1.—Single kidney located in the pelvis, as found in our case No. 534092, reveals type of associated urinary tract anomaly that must be looked for.

Competition now developed between the exponents of the Baldwin technique and the operation devised by Schubert⁷ wherein the lower rectum, except for the anal orifice and sphincter, was moved forward to function as a vagina (Fig. 3). The continuity of the alimentary tract was restored by pulling down and attaching the lower cut end of the sigmoid to the anal ring. This method was popular among European gynecologists and was considered less formidable and, therefore, less hazardous than the procedure advocated by Baldwin. By 1927, Schubert was able to report a mortality of only 3.2 per cent as compared with a 17 per cent mortality rate for the Baldwin operation. The fact that Wagner² reported a case of vaginal aplasia treated by Schubert's method where the patient later successfully gave birth to three children further served to boost the popularity of this operation. Doubtless both of these techniques would have increased in popularity had not the associated mortality and morbidity continued to serve as a sobering influence. These same drawbacks, however, served to stimulate development of other, less hazardous, plastic procedures, and during the next quarter century there appeared numerous new operative techniques. Most of these called for dissection of a channel between the bladder and bowel plus the lining of this channel with skin derived either from the labia (Graves,⁸ Davis and Cron,⁹ Falls¹⁰) or from the thigh (Frank and Geist,¹¹ Grad,¹² Dannreuther,¹³ Flynn and Duckett¹⁴) (Figs. 4, 5, and 6). Many variations in all of the basic techniques resulted as time went on. This plastic era was characterized by reduced mortality if not by brilliance and usefulness of the results obtained. We cannot speak for others, but, in

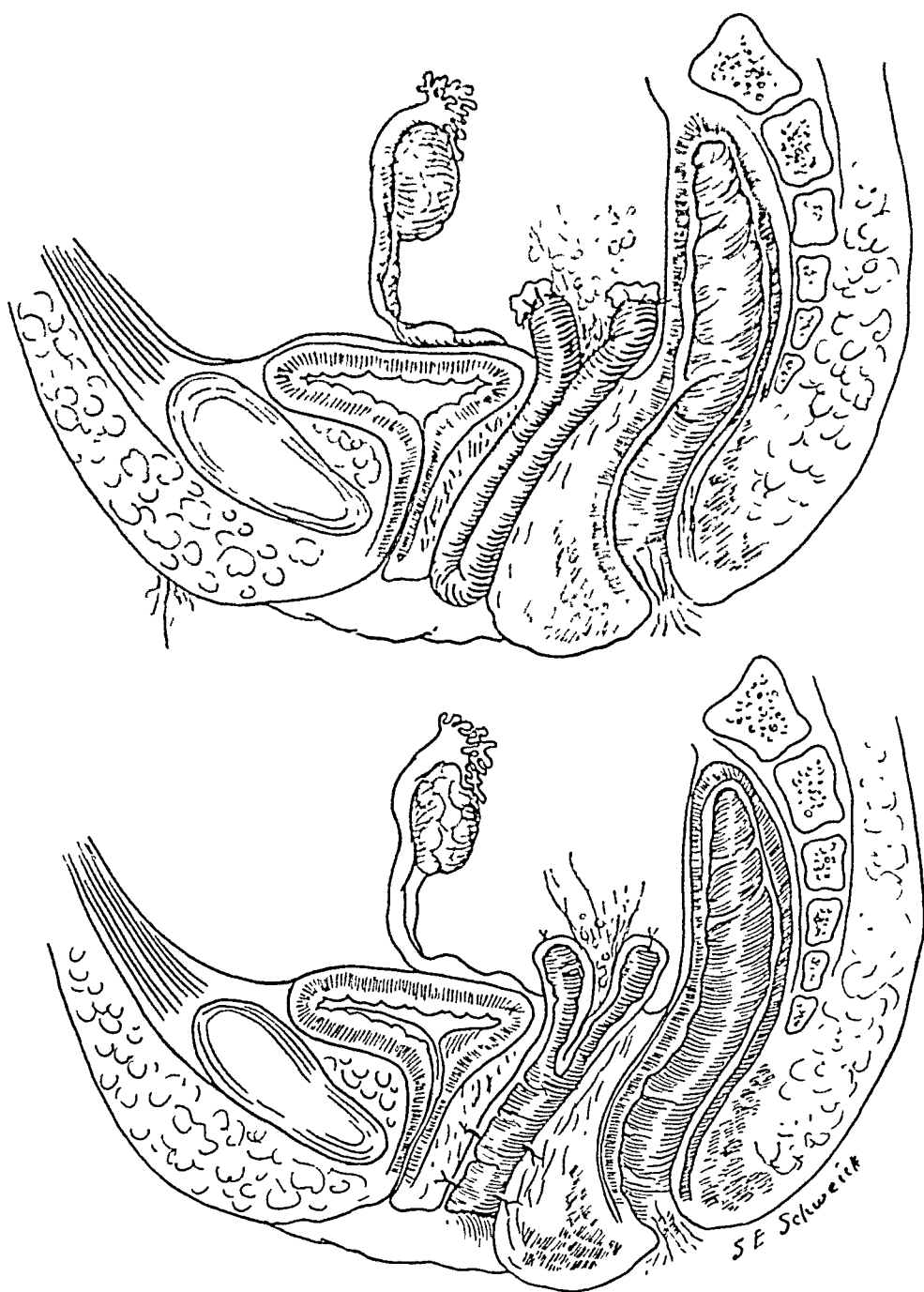


Fig. 2.—Baldwin operation: illustrating use of terminal ileum in formation of new vagina.

our hands, the results following these cumbersome "satchel-handle" tube grafts or the use of labial skin were not satisfactory. The plastic procedures nevertheless represented a forward step in the evolution of a safer and more acceptable method of treatment.

It had long been known that pressure, properly directed and over a sufficient length of time, ultimately produced a vaginal channel of some depth. Frank¹⁵ re-emphasized this principle in 1938 (Fig. 7). Simplification of surgical treatment, however, was given a real boost when, in 1935, Wells¹⁶ reported the use of petrolatum-gauze packing in a dissected vaginal channel. The vaginal gauze was replaced every forty-eight hours and, at the end of one month, he noted that the mucous membrane had grown up into the channel for a distance of 1 inch. Two subsequent deeper dissections, each followed by packing, ultimately led to the formation of a 4-inch epithelium-lined vaginal tube. In 1938, Wharton¹⁷

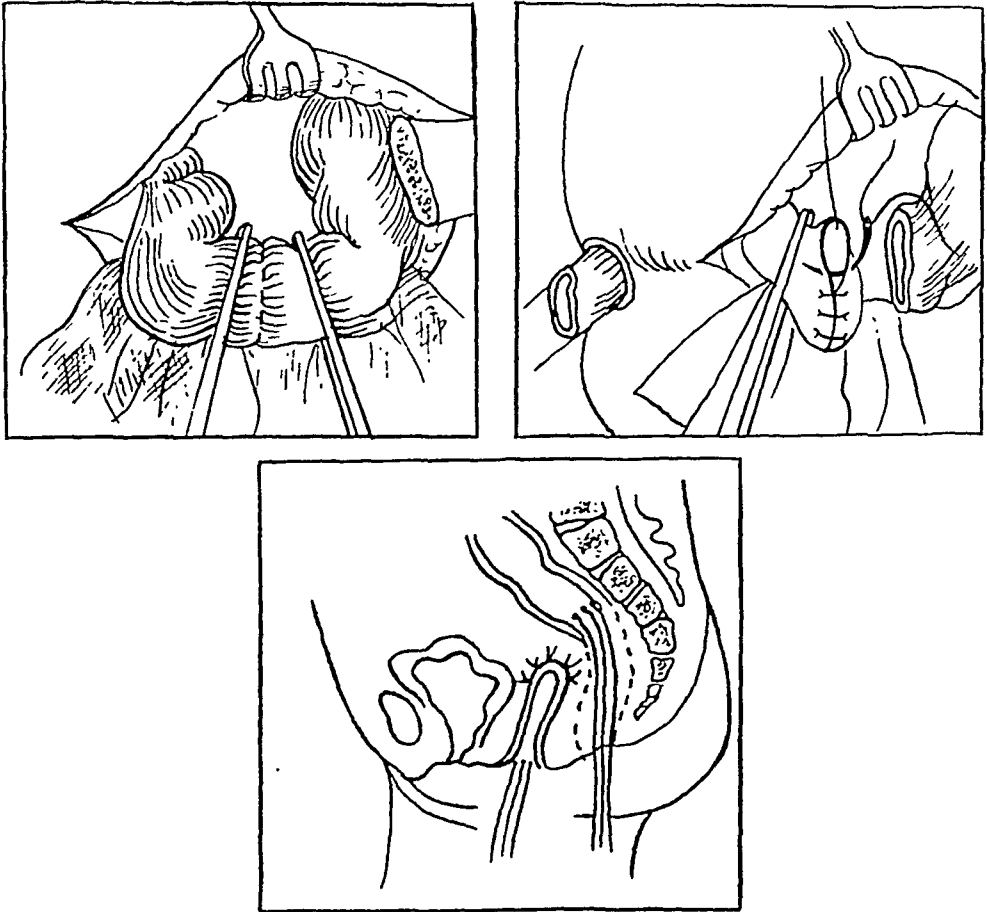


Fig. 3.—Schubert type operation.

emphasized the remarkable proliferative power of the vaginal or vestibular mucous membrane and outlined his method of treatment. This consisted of the usual dissection between the bladder and rectum and the maintenance of patency for at least three months by the use of a wax-filled condom or balsa wood mold. Wharton described four cases successfully treated by this method. In 1940, he reported twelve so treated by seven different surgeons with successful outcome in each case. He also emphasized the importance of postoperative care.

Kerschner and Wagner² used Thiersch grafts sutured over a rubber sponge and placed into the newly dissected channel. On removing the sponge, eight to ten days later, the grafts were seen to have taken. Dilators were subsequently used to prevent contraction. Barrows¹⁸ favored this procedure because there was no serious morbidity. No scars

of any significance remained and there was no prolonged hospitalization. Furthermore, the new lining closely resembled normal vaginal mucous membrane. Barrows described two patients so treated and stated that in thirty-two collected cases poor results occurred only twice.

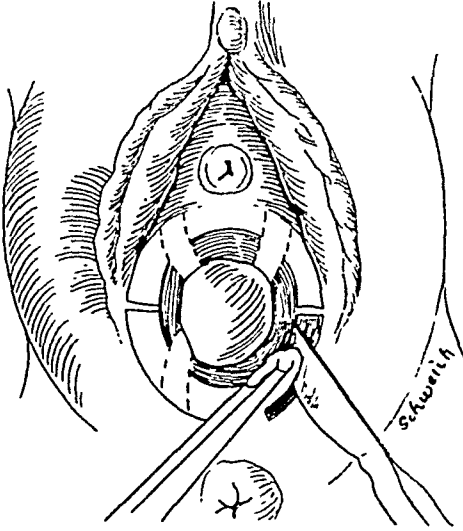


Fig. 4.

Fig. 4.—For lining newly dissected channel, Falls used mucous membrane flaps obtained from the vestibule.

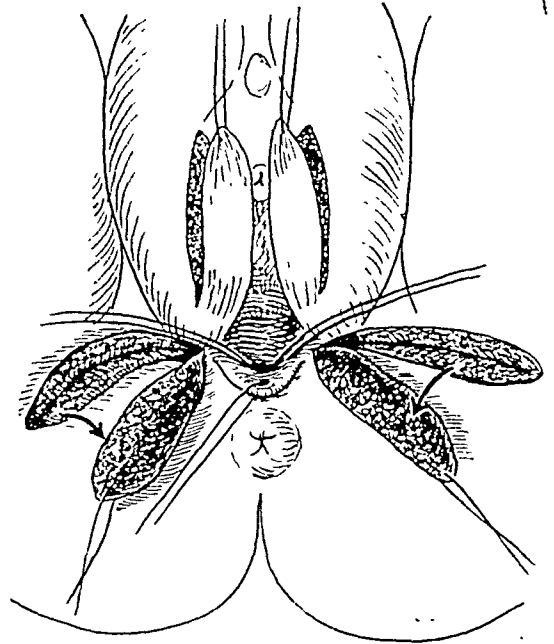


Fig. 5.

Fig. 5.—Illustrating use of skin flaps for lining newly dissected vaginal channel as described by Douglass in 1934.

In July, 1938, McIndoe and Bannister¹⁹ reported using a thin skin graft over a vulcanized mold inserted into the newly dissected vaginal channel with complete take of the graft. Ultimately, a normal looking vagina was produced. An obturator was left in for three months in order to prevent contraction. Counseller²⁰ popularized this procedure in this country and in 1938 reported on his experience by this method. In 1944 Counseller and Sluder, Jr., recorded thirty-five cases treated by this method. Reports of cases similarly treated are appearing with more and more frequency and with generally favorable comment as to the results obtained. We, too, have used the split thickness skin graft method with good results.

Treatment of congenital aplasia of the vagina has now progressed to the stage where it no longer is necessary to deny treatment to any girl with this

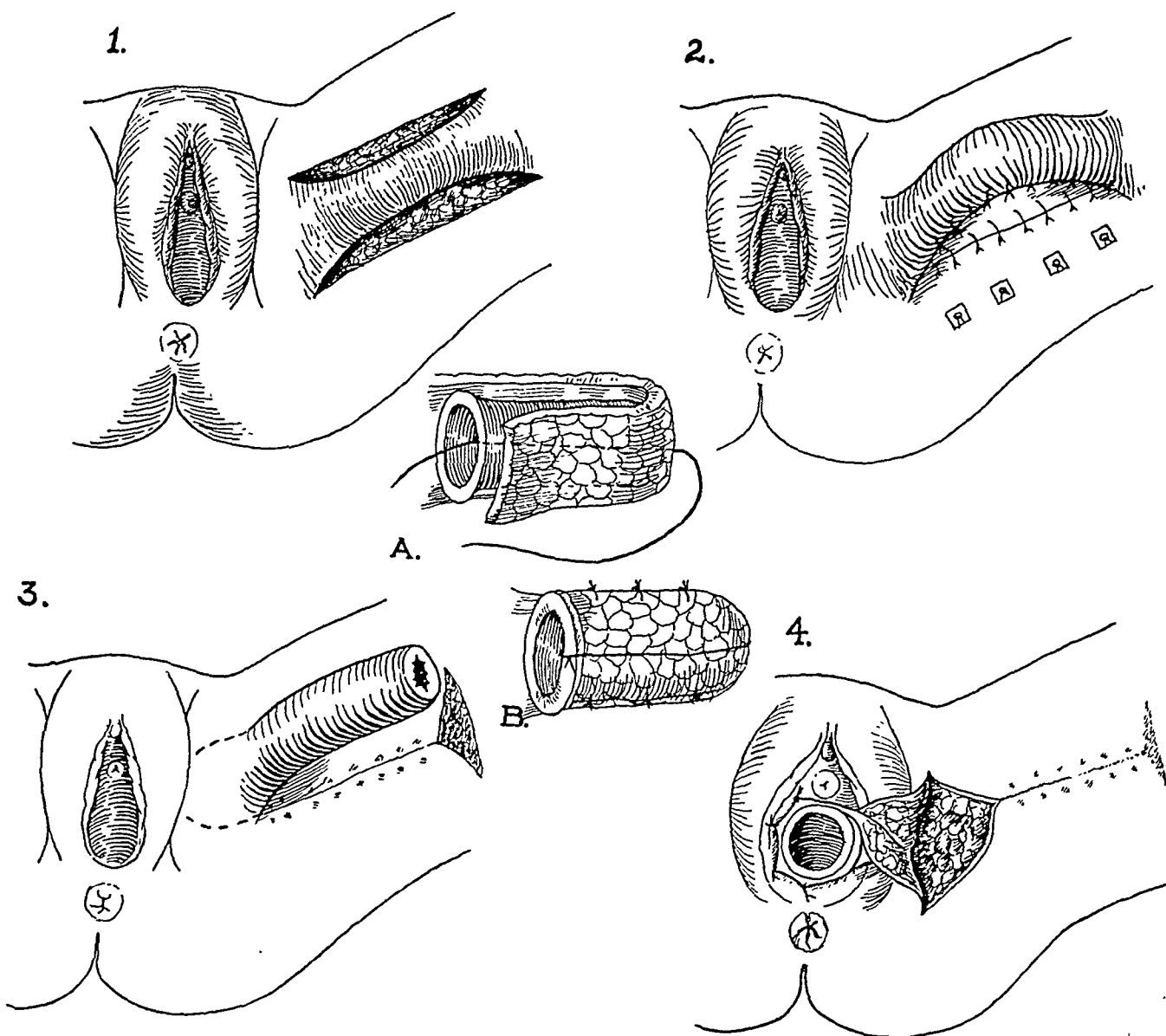


Fig. 6.—Illustrating the Frank-Geist "satchel-handle" type tube graft operation. Extensive long-drawn-out plastic procedures of this type are no longer necessary or desirable.

condition, nor is it necessary to wait until the young woman has had an offer of marriage before proceeding with treatment. Indeed, when correction is made dependent on an offer of marriage, it emphasizes the abnormality and increases the psychological drawbacks which commonly go with anomalous congenital development of any kind.

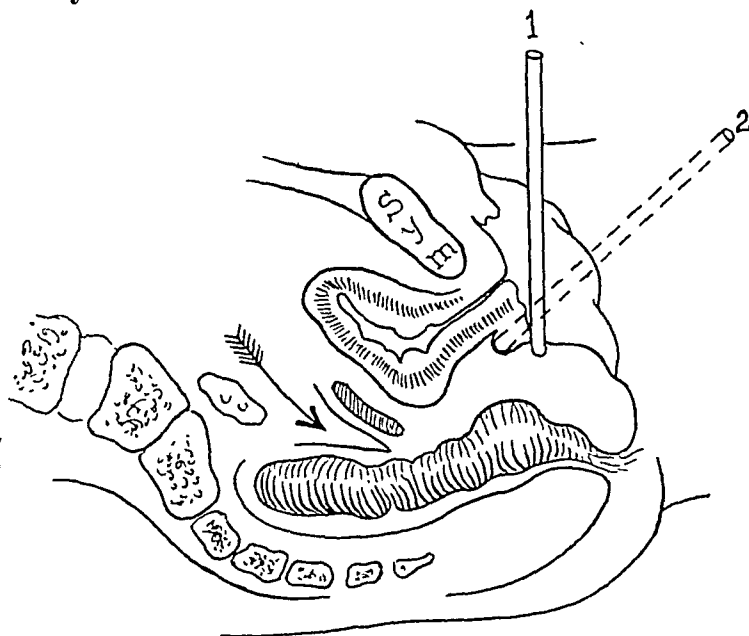


Fig. 7.—Nonsurgical pressure correction of congenital vaginal aplasia as described by Frank in 1938.

Our interest in congenital aplasia has been twofold. Like many others we wished to know the most satisfactory and the simplest method of correction. To this end we reviewed the literature and decided, some years ago, on the basis of this review as well as on the past experience of the senior author, that, while no one method might be universally acceptable, all evidence, including our own experience, pointed with preference to one of two procedures. Either the formation of a channel between bladder and bowel and the continued use of an obturator until epithelization had taken place by ingrowth from the vestibular epithelium, or else dissection and the use of a split-thickness skin graft-covered obturator such as advocated by Kerschner and Wagner, Barrows, McIndoe and Bannister, Counseller, and others. During the past decade we have used both methods and, in this report, present the results in our series of seventeen cases (See Table I).

Our second interest in this problem was to learn something of the behavior of the transplanted epithelium in those cases where a skin graft was used in lining the dissected channel.

Before listing our results and data, however, we present in brief outline the steps followed in the correction of our cases.

1. Careful history and physical examination, including intravenous pyelograms and such other studies as may be desirable in order to rule out associated anomalies of the genito-urinary tract.
2. Customary preoperative preparation: enema, catheterization, etc.
3. General anesthesia.

TABLE I

SERIES NO.	CASE NO.	GENERATIVE ORGANS PRESENT			TYPE OF OPERATION		RESULTS	COMMENTS
					DISSECTION, OB-TURATOR ONLY	DISSECTION, SKIN GRAFT ON OBTURATOR		
1	426577	Absent	Absent	Present		Yes	Unsatisfactory	Slough of graft severe reaction due to plastic obturator. Fistula for few days. Now married. Tender scarred vagina
2	476743	Deep vestibular pouch	Absent	Present		Yes	Satisfactory	
3	486286	Absent	Absent	Present		Yes	Satisfactory	
4	497804	Absent	Absent	Present		Yes	Satisfactory	
5	474074	Shallow vestibular pouch	Present	Present		Yes	Satisfactory	Slight scarring near cervix
6	510921	Lower half absent, upper half of a hematomocolpos	Present	Present	Yes		Satisfactory	
7	511392	Absent	Absent	Present		Yes	Satisfactory	Vagina not full length
8	529316	Slight vestibular pouch	Absent	Present	Yes		Unsatisfactory	Required dilatation. Ultimate result good
9	529599	Slight vestibular pouch	Absent	Present			Satisfactory	
10	537113	Absent	Absent	Present	Yes		Satisfactory	
11	545507	Tiny channel $\frac{1}{8}$ " diameter	Present	Present	Yes		Unsatisfactory	Patient was pseudohermaphrodite reported as Case 12
12	545507	Reoperation—same patient as No. 11			Yes		Satisfactory	
13	534092	Absent	Absent	Present		Yes	Satisfactory	Only one kidney located in pelvis
14	312924	Absent	Absent	Present		Yes	Satisfactory	
15	562787	Slight vestibular pouch	Present	Present		Yes	Unsatisfactory	Required dilatation. Ultimate result good
16	568002	Pouch produced by first marriage	Absent	Present		Yes	Satisfactory	
17	566545	Pouch and tiny channel to cervix	Present	Present	Yes		Satisfactory	Good result

4. If a skin graft is to be used, it may be obtained at this time. We prefer a split thickness graft, 12 to 15 thousandths of an inch thick, taken either from the abdomen or the thigh. The use of a Padgett or other type dermatome and a good sticky mastic greatly facilitates this part of the operation. The graft obtained should be adequate to permit covering the obturator.

5. Dress wound site from which graft was taken.

6. Patient is now placed in lithotomy position, and genitalia carefully reinspected.

7. A transverse incision is now made in the vestibular mucosa about midway between the external urinary meatus and the posterior vaginal fourchette.

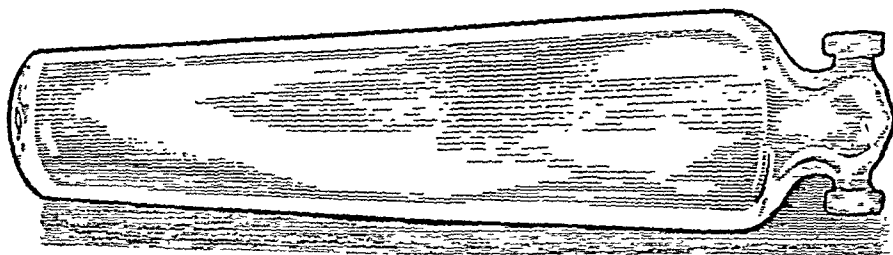


Fig. 8.—Obtutors made of glass (nonbreakable when possible) and in several sizes are highly desirable in the treatment of vaginal aplasia.

8. The dissection is carried up—blunt dissection preferred—between the rectum and bladder. Once the cleavage line is found, dissection may be accomplished without difficulty and carried up the cervix, if present, or else to the peritoneum.

9. Gross bleeding is controlled by ligature and pack. If the pack is left in while the graft is being placed on the obturator, the oozing may be reduced.

10. Pack is now removed from the dissected channel and the graft-covered obturator inserted into the dissected channel where it is held in place by a perineal pad and T binder.

11. Place an indwelling catheter in the bladder which may be removed when the obturator is taken out on the seventh to tenth postoperative day.

12. Postoperative care involves no special problems except that it is well to limit solid food intake during the first few days.

13. On the seventh to the tenth day the obturator is gently removed and the newly formed epithelium-lined vaginal channel carefully inspected and irrigated with warm saline. This is easily accomplished since it is possible to insert a bivalve speculum and look over the new-formed channel without discomfort to the patient.

14. The obturator, after it has been cleaned and covered with a lubricant, is now reinserted. The patient may be up and about and is taught to remove the obturator (while in bed so that she does not drop and break it) before defecating and before voiding. Reinsertion is carried out in bed so the chance of breaking is minimized. In the postwar period obturators should be made of nonbreakable glass or plastic (Fig. 8).

15. The patient is discharged on the tenth or twelfth postoperative day, or whenever convenient, but should wear the obturator regularly until re-examined, usually in four to six weeks. Further use of the obturator after this period of time will depend on the findings at subsequent examinations. As a rule, however, when the obturator is discontinued, the patient should be cautioned to wear it at night until she is able to determine whether its nonuse during the day leads to increased difficulty in reinsertion. If this be the case, continued use of the obturator both day and night is warranted.

16. In patients with underdeveloped secondary sex characteristics the use of estrogen therapy may be helpful during the postoperative period as a means of stimulating epithelial growth.

17. The taking of a skin graft is obviously omitted in those cases where only dissection and the use of an obturator are planned. This procedure is not difficult if care be taken in finding the proper line of cleavage between bladder and bowel.

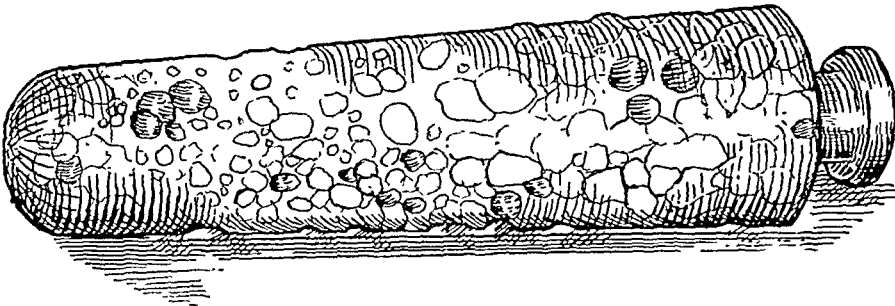


Fig. 9.—Plastic obturator once used by us. Note marked irregularity of the once smooth surface due most likely to some chemical reaction between mastic used to hold skin graft in place and plastic material in obturator. Complete destruction of skin graft occurred in this case.

In one of our early cases a plastic obturator was used (Fig. 9). As a result of some destructive chemical reaction, the entire graft was destroyed and the obturator, which had been perfectly smooth prior to use, was badly pock-marked. The tissue necrosis was so severe that the patient developed a vesico-vaginal fistula which, fortunately, underwent spontaneous healing after a few days. After many months of wearing a glass obturator, this patient finally presented a completely epithelized channel, but there was not the pliability or softness that one sees in a completely successful result. The patient has since married and has a usable, though somewhat tender, vaginal tube. In this case, and in cases reported by Wells and Wharton, it is clear that the vestibular epithelium shows marked proliferative propensities, sufficiently so to permit epithelization of the dissected channel.

In order to compare the two procedures, we used the Wharton technique of dissection and the insertion of an obturator without skin graft in six of our seventeen cases. Table I shows a comparison of end results. Our standard for a successful result was an epithelized, soft, pliable vaginal tube showing no unusual or excessive amounts of scar tissue or contraction after a reasonable convalescent period (three months). While our experience is not extensive (17 cases), we feel that the use of a skin graft is definitely superior and, unless further experience and compiled evidence warrants, we shall give preference to this combined procedure in those patients reporting for treatment in the future. We recognize, however, that in some instances, especially where there

is only partial absence of the vagina, dissection and the use of an obturator may be an entirely adequate, and indeed, may even be more desirable than the combined method.

While choice of operation is important, the actual behavior of the epithelium in the new-formed vagina is also of interest. In February, 1942, we had an opportunity to observe one of our grafted patients (No. 474074) one year after operation, throughout a complete menstrual cycle. Vaginal smears

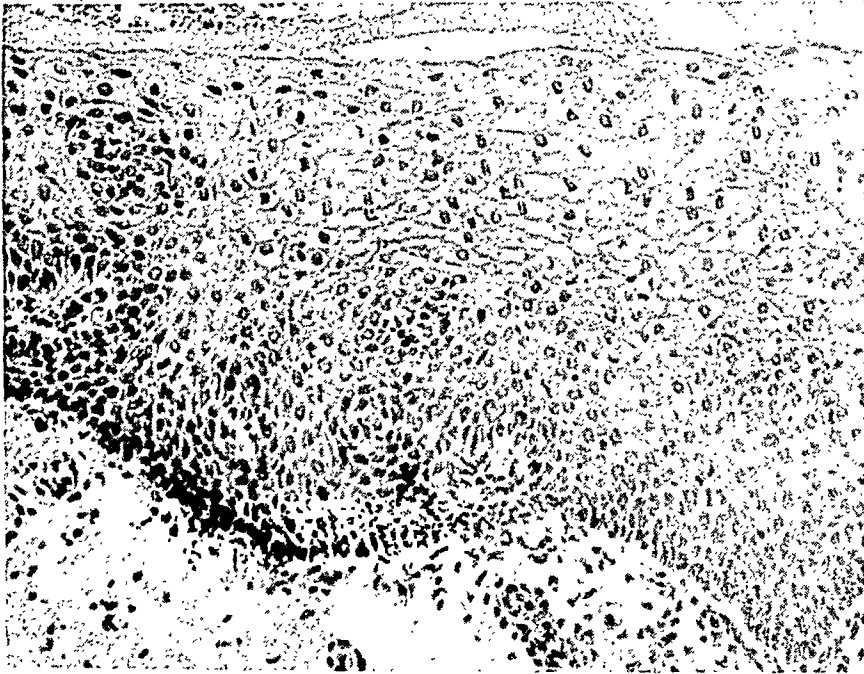


Fig. 10.—Vaginal biopsy taken on twelfth day of cycle ($\times 260$). Note typical mucous membrane appearance. Compare with Fig. 11.



Fig. 11.—Skin biopsy taken from thigh near site from which graft for vagina was obtained. Both vaginal and skin biopsies were taken on the twelfth day of cycle ($\times 260$).

were carefully studied. In addition, several biopsies were taken from the year-old vagina and, for comparison, from near the site where the skin graft had originally been obtained. Gross inspection of the vagina at this time showed a normal-appearing, pink, mucous membrane. The surface was moist, but somewhat less rugous than is normally seen. Biopsy and histologic examination showed stratified squamous epithelium of the mucous membrane type, indistinguishable from normal vaginal mucosa (Fig. 10). The basal layer was composed of small germinative cells, above which the cells became progressively more cornified toward the surface. No keratin was present. The submucosal tissue was fibromuscular without the accessory skin structures. Daily vaginal smears stained by the Shorr technique revealed cells which could not be differentiated from those of normal vaginal epithelium. There was a gradual increase in cornification and a decrease in the number of leucocytes until the twelfth day of the cycle, when there was a complete leucopenia at the peak of cornification. On the following day the leucocytes suddenly reappeared in large numbers, and during the remainder of the cycle the smears all contained leucocytes and some folded and fragmented epithelial cells. This cycle of events is exactly the same as that which occurs in the vagina of normal menstruating women and which has been utilized in the study of ovarian function. Smears stained for glycogen by the iodine vapor method of Mack²¹ showed normal amounts of glycogen to be present. There was a gradual increase in the glycogen content until the peak of estrogen stimulation on about the twelfth day of the cycle, after which it diminished. Vaginal biopsies taken on the twelfth day of the cycle and stained by the Best carmine technique showed glycogen to be present in the outer cell layer. For purposes of comparison, sections of skin were taken from near the site where the graft had been obtained. Both biopsies were taken on the twelfth day of the cycle. Histologic examination revealed normal skin with glands, hair follicles, and surface keratin layer (Fig. 11). Glycogen could not be demonstrated in the skin biopsy. Later, a total of 18 mg. of stilbestrol in oil was applied over a period of six days to a small area on the thigh, but microscopic examination of tissue taken from this site at the completion of the treatment showed no change either in cell type or in thickness of the epithelial layer. Glycogen could not be demonstrated in the biopsies from this area by the Best carmine technique.

The normal vagina, with the exception of the lowermost portion, probably represents an invasion of urogenital sinus epithelium and, despite the resemblance of vaginal epithelium to other stratified squamous epithelium, its physiology is unique. The generative tract is the only place where the control of glycogen deposition is, at least in part, an important function of the estrogenic hormone. The normal skin from the thigh transplanted into the artificially produced vaginal channel appears to assume the functions of normal vaginal mucous membrane. In the case here reported, and in the case reported by Whitacre and Wang²² the skin lining the new tract appears to acquire the histologic, as well as the physiologic, characteristics of normal vaginal mucous membrane. Replacement by ingrowth of vestibular epithelium cannot be en-

tirely ruled out but this appears unlikely since the graft took completely and no evidence of tissue loss could be demonstrated on subsequent examinations.

As further confirmation in proving the persistence and functional activity of transplanted skin, we hoped for an opportunity to correct this anomaly in a Negro girl. It was felt that if the black pigment in the skin taken from the thigh or abdominal wall remained after being grafted into the new-formed vaginal channel and functioned as vaginal epithelium, this additional evidence would permit the concession that, under certain circumstances, transplanted skin may undergo physiologic and environmental response to a degree previously considered unlikely. It is improbable that a reversal of this situation would have any practical application but it would be of interest to know how well vaginal mucosa might function as a substitute for normal skin.

References

1. Quoted by Whitacre, Frank E., and Chen, C. Y.: *AM. J. OBST. & GYNEC.* 49: 789, 1945.
2. Steinmetz, Eugene P.: *West. J. Surg.* 48: 169, 1940.
3. Counseller, Virgil S., and Sluder, Fletcher S., Jr.: *S. Clin. North America* 24: 938, 1944.
4. Baldwin, James F.: *Am. J. Obst.* 56: 636, 1907.
5. Mueller, A.: *Prag. med. Wehnschr.* 34: 626, 1909.
6. Mori, M.: *Zentralbl. f. Gynäk., Leipz* 33: 172, 1909.
7. Schubert, G.: *Zentralbl. f. Gynäk.* 33: 1017, 1911.
8. Graves, W. P.: *Gynecology*, ed. 1. Philadelphia, 1916, W. B. Saunders Co., p. 567.
9. Davis, Carl Henry, and Cron, Roland S.: *AM. J. OBST. & GYNEC.* 15: 196, 1928.
10. Falls, Fred: *AM. J. OBST. & GYNEC.* 40: 906, 1940.
11. Frank, Robert T., and Geist, S. H.: *S. Clin. North America* 12: 305, 1932.
12. Grad, Herman: *Surg., Gynec. & Obst.* 54: 200, 1932.
13. Dannreuther, Walter T.: *AM. J. OBST. & GYNEC.* 35: 452, 1938.
14. Flynn, C. W., and Duckett, J. W.: *Surg., Gynec. & Obst.* 62: 753, 1936.
15. Frank, Robert T.: *AM. J. OBST. & GYNEC.* 35: 1053, 1938.
16. Wells, W. F.: *Am. J. Surg.* 29: 253, 1935.
17. Wharton, L. R.: *Ann. Surg.* 107: 842, 1938.
18. Barrows, David H.: *AM. J. OBST. & GYNEC.* 31: 156, 1936.
19. McIndoe, A. H., and Bannister, J. B.: *J. Obst. & Gynaec. Brit. Emp.* 45: 490, 1938.
20. Counseller, Virgil S.: *AM. J. OBST. & GYNEC.* 36: 632, 1938.
21. Mack, Harold: *Harper Hosp. Bull.* 1: 54, Jan. 1942.
22. Whitacre, Frank E., and Wang, Y. Y.: *Surg., Gynec. & Obst.* 79: 192, 1944.

HYPERTROPHY OF THE UTERUS*

ARTHUR H. CURTIS, M.D., CHICAGO, ILL.

*(From the Department of Obstetrics and Gynecology, Northwestern University
Medical School)*

ENLARGEMENTS of the uterus other than those caused by tumorous growths have heretofore been designated by various terms according to the etiological and pathologic factors concerned. "Hypertrophy of the uterus" is an all-inclusive descriptive term which serves to group these various enlargements into a much needed clinical entity.

Hypertrophy of the uterus is characterized by morbid enlargement or overgrowth, particularly of the body of the uterus. It presents a pathologic complex which continues to cause much confusion among gynecologic pathologists as well as gynecologists. Nonetheless, it may well be considered as an entity, despite the various etiological factors involved and the protean picture presented.

In cases of hypertrophy the uterus is symmetrically enlarged† and heavy, or the plump, firm, ovoid corpus alone may be the chief site of change. The uterine walls are thickened, often to 3 cm. or more, the cavity enlarged beyond its usual capacity. The cut surface of the uterine wall tends to be firm and rigid, the texture tough and striated, in a measure justifying the term "fibrotic," a favorite designation which has been criticized as elusive and unwarranted except as a pathologic rarity. The blood vessels may be numerous and prominent, notably the veins, which frequently are enlarged or are seen with the naked eye as tufted nodules simulating those of adenomyosis.

The endometrium varies greatly, depending on the etiological factors concerned. It may be entirely normal or may be thickened or even polypoid in case there is hormonal imbalance or obstructed uterine drainage.

Associated with the changes in the uterine corpus, numerous and varied changes occur in the cervix, in Mackenrodt's ligaments, in the ovaries, and in the other pelvic tissues, dependent upon the etiology of the hypertrophy and the severity and duration of the process. Changes in the ovaries are naturally reflected in the uterus in so far as hormonal function is disturbed.

Classification of the etiology and pathologic histology of hypertrophy of the uterus has been difficult and unsatisfactorily, in part owing to attempts to limit the number of etiological factors believed to contribute to this pathologic complex; also because the role played by endocrine disturbances, entirely unrecognized in earlier years, is still an undetermined although very important factor. Years of floundering eventuated, some years ago, in rather wide accept-

*Read at the meeting of the Chicago Gynecological Society, May 18, 1945.

†Anatomic descriptions of the uterus invariably omit mention of the thickness of the healthy multiparous uterine wall, which normally measures approximately 2 cm. in the region of the greatest diameter of the uterine corpus. This basic measurement is important in evaluation of the pathologic changes to be considered in the subject under discussion.

ance of certain entities among these benign enlargements of the uterus: the old term "fibrosis uteri" became replaced by "chronic subinvolution," "true chronic metritis," and "diffuse hypertrophy of the uterus." Then, in more recent times, with recognition of the dominating influence of the hormones, the entire subject became more confused; it is currently accepted that endocrine changes account for most cases of *diffuse* hypertrophy of the uterus and also play some part in the other hypertrophies.

As a matter of fact, numerous etiological factors are concerned with hypertrophy of the uterus, just as many factors may be responsible for enlargement of any other viscus, such as the kidney, or any other unit of the human anatomy, such as the leg. In evaluating the etiology and pathology, specific local factors of influence must not be overlooked. These include menstruation and pregnancy and the hormonal changes associated therewith, also the normal and abnormal ovarian and relatedcretory activities at other times.

Normal puerperal involution was first described by Szasz-Schwarz.¹ In the process of involution after childbirth, with gradual degeneration of the hypertrophic blood vessels much elastic tissue always persists in the parous uterus. There are circular or crescentic collars of elastic tissue around the arteries of the inner zone of the uterine wall, thick vessels largely due to elastic tissue in all layers of the vessel walls in the middle zone, and increased subperitoneal and vascular elastic tissue in the outer zone of the uterus, where the veins are also thick walled, elastic tissue in great preponderance. This process is diagnostic of a previous pregnancy, never appears in the nulliparous uterus, and increases with each succeeding pregnancy. The process in cases of chronic subinvolution is partly physiologic, partly pathologic. Chronic subinvolution presents an exaggeration of normal physiologic involution, either with or without infection. It is chiefly ascribable to an endocrine factor except in those cases in which there is histologic evidence of infection, notably round cells, plasma cells, and increased connective tissue.

All clinicians are conversant with the appearance of a massive, hypertrophic, badly retrodisplaced uterus in a woman who has borne many children. This may be cited as an example of chronic subinvolution, but it may equally well be called diffuse hypertrophy. Similarly, in lesser degree, a badly retrodisplaced nulliparous uterus may also present a picture of diffuse hypertrophy. Microscopically, an excess of elastic tissue characterizes chronic subinvolution, whereas diffuse hypertrophy presents, theoretically, a proportionate increase in the various elements of the uterine wall, i.e., overgrowth of the muscle, the connective tissue, and the blood vessels. If there is associated endometrial hyperplasia, overgrowth of the various tissues may well be due to an endocrine factor. Changes of this sort, involving all elements of the uterus, are readily produced by prolonged excessive administration of estrogens.

A variant from chronic subinvolution and diffuse hypertrophy of the uterus is chronic metritis. Use of this term is preferable in those instances in which there is a grossly evident infection of the tubes, ovaries, or pelvic cellular tissues, or a history of puerperal or postabortive infection, histologic examination of the uterus presenting the usual residual evidence of an inflammatory process.

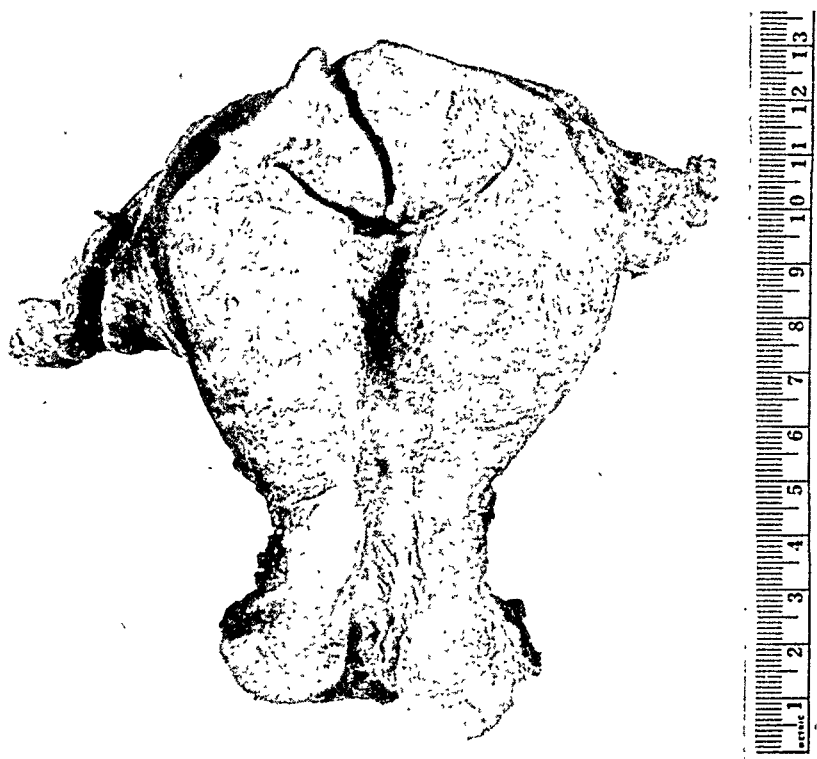


Fig. 1.—Hypertrophy of the uterus, the entire corpus involved. Length 13 cm., greatest breadth 9 cm., thickness of wall of body of uterus 3.8 cm. A typical instance of hypertrophy of connective tissue and uterine musculature, the blood vessels numerous and prominent with marked increase in connective tissue and elastic fibers evident on microscopic examination.

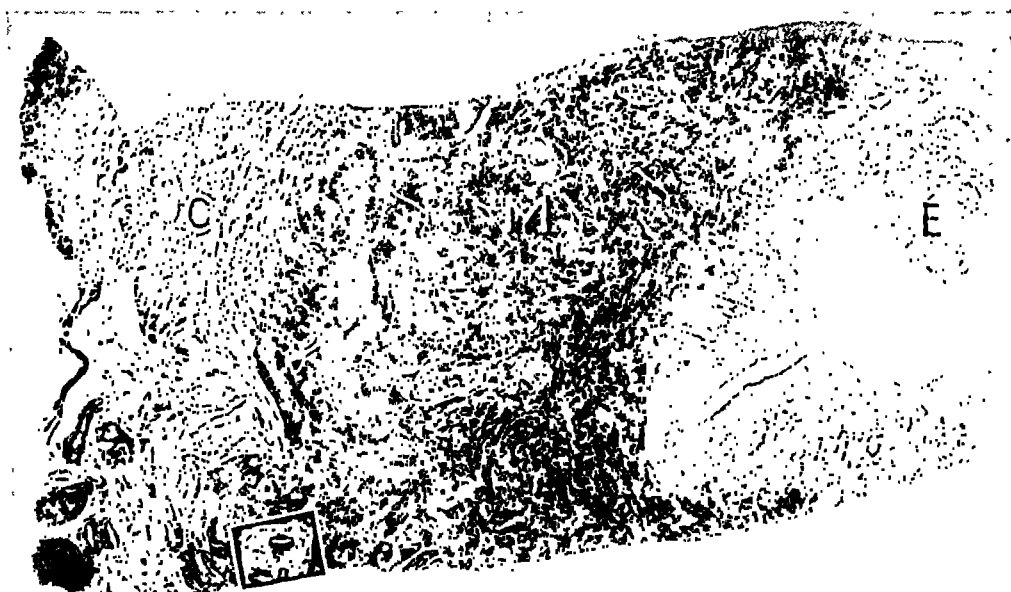


Fig. 2.—Hypertrophy of the uterus. Section through entire thickness of uterine wall showing (C) connective tissue replacement of musculature of outer third of uterine wall, (M) hypertrophy of remaining musculature, (E) hyperplasia of endometrium (trichrome stain). ($\times 2\frac{1}{2}$.)



Fig. 3.—Hypertrophy of uterus. Section shown in area indicated by square in Fig. 2, revealing massive hypertrophy of elastic tissue (Verhoeff metanil yellow stain). ($\times 43$.)

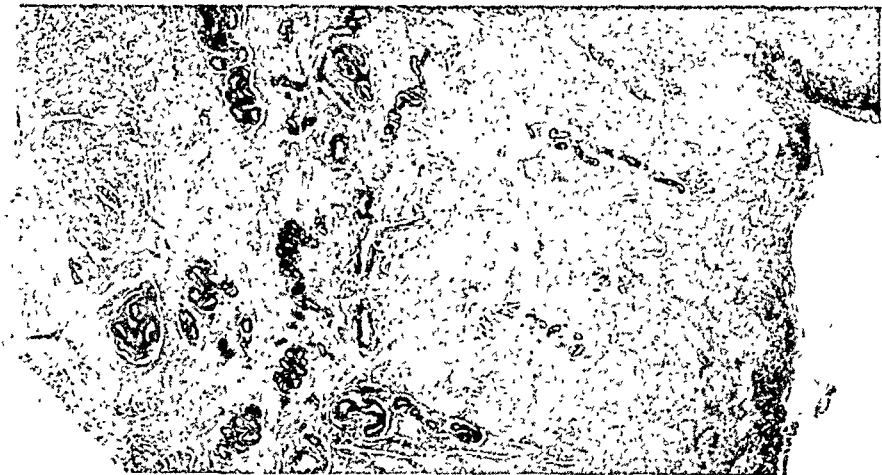


Fig. 4.—Hypertrophy of uterus, section through uterine wall. Hypertrophy of vascular and perivascular elastic tissue (Verhoeff-Van Gieson stain). ($\times 2\frac{1}{2}$.)

Diagnosis of Hypertrophy of the Uterus

The usual symptoms are prolonged or excessive menstruation, pelvic pressure with more or less aching discomfort, and increased vaginal discharge.

Examination reveals an enlarged uterus, which is usually heavy and often retrodisplaced and is difficult to differentiate on bimanual examination from adenomyosis of the uterus or diffuse enlargement from deeply buried myomas. Differentiation from carcinoma of the body of the uterus is sometimes difficult, occasionally even after examination of uterine curettings in those cases of hypertrophy with marked endometrial hyperplasia.

Histologic diagnosis of the various types of uterine hypertrophy is facilitated by differential stains. With routine hematoxylin and eosin stain, enlarged and thickened blood vessels and the amount of perivascular connective tissue are readily recognized, but accurate determination of the relative proportion of connective tissue and muscle cells is not simple. A trichrome stain, similar to the Mallory stain, developed in our laboratory by Miss Milligan, helps to solve this difficulty; the muscle cells and nuclei are stained red by acid fuchsin, the connective tissue clearly distinguished by fast green, the blood cells revealed in various shades of orange by orange G. In this connection, it is to be noted that differential stains must not be depended on implicitly, because degenerated tissue produces peculiar staining reactions and may lead to errors. Elastic fibers are recognized solely by special stains. Of these, the Verhoeff, preferably with metanil yellow counterstain, has been most satisfactory in our hands in the staining of formalin-fixed tissues. The orcein-Van Gieson stain has been less dependable for tissues fixed in formalin.

The more we study enlarged uteri, the more apparent it becomes that various gradations of hypertrophy are encountered in most instances and that pure subinvolution or true diffuse hypertrophy or hypertrophy due solely to metritis or to endocrine disturbance is unusual.

Treatment

Curettage may be required for differential diagnosis, and, strangely enough, it is sometimes beneficial. If more important surgical intervention is required, one should hesitate to perform corrective operations for uterine displacement in these cases unless childbearing is an important issue; removal of the offending organ by subtotal or complete hysterectomy is the procedure of choice.

Reference

1. Szasz-Schwarz, Hugo: *Recherches sur les Alterations Seniles des Vaisseaux Sanguins et sur le Tissu Elastique de l'Uterus*, *Revue de Gyn.* 7: 593, 1903.

ANEURYSM OF THE SPLENIC ARTERY WITH RUPTURE, A RARE COMPLICATION OF PREGNANCY

W. C. DANFORTH, M.D., EVANSTON, ILL.

(From the Evanston Hospital)

ANEURYSM of any sort is a rare complication of pregnancy. Aneurysms as a rule are found in individuals who are older than the great majority of expectant mothers. Aneurysms of the aorta of any sort are uncommon and aneurysms of its branches make up an extremely small part of the total of all aneurysms.

The following case, which illustrates a complication extremely rare during pregnancy, is reported.

A woman, aged 28 years, gravida iii, entered the hospital at the end of the seventh month complaining of severe upper abdominal pain. There was no external hemorrhage. Abdominal and pelvic examination were quite negative. All the usual signs of severe blood loss were present. She entered in the afternoon. On the following morning her condition was worse and heart tones were no longer to be heard. At this time she complained of tenderness over the uterus. Because it was feared that a premature detachment of the placenta might have occurred, it was decided to empty the uterus. This was done by vaginal hysterotomy. A dead fetus was removed but no sign of detachment was found. Transfusion was done. About midnight of this day sudden collapse followed by death occurred. Wassermann was negative.

The autopsy disclosed a massive hemorrhage into the peritoneal cavity, there being about $3\frac{1}{2}$ liters of blood present. An enormous retroperitoneal hematoma was found which extended up to the level of the kidney. The aneurysmal sac was 1.5 cm. in diameter and contained clotted blood adherent to the lining of the sac. Blood had escaped at first from the wound in the aneurysm into the lesser peritoneal sac and later into the general peritoneal cavity. The wall of the aneurysm showed areas of necrosis in the intima and adjacent media. The tissue in these places was infiltrated with leucocytes and the elastic tissue was completely lost. Sections stained by the Levaditi method show no spirochetes.

A second case of aneurysm of the splenic artery not associated with pregnancy was seen recently on the medical service in this hospital. This patient was a woman of 62 years. She entered, complaining of abdominal pain unrelated to anything. After a number of days of observation, during which the cause of the pain remained undetermined, operation was decided upon. Exploration disclosed a mass in the upper right abdomen which was found to be an aneurysm of the splenic artery. This was removed, the artery being ligated on both sides of the arterial enlargement. The mass which was removed was 2 by 1.3 by 1 cm. It was smooth and yellow and consisted of the wall of a cystic cavity. There were extensive areas of calcification in the wall and marked thickening of the intima. Kline test was negative. Death followed in a few hours.

Baumgartner and Thomas, in 1924, stated that forty cases could be found in all available literature in fifty years. Of these, 19 were males, 16 females, and in 5 cases the sex was not stated. The size of the aneurysm in this series varied from the size of a cherry to that of a hen's egg. Of the entire number, 33 were first found at autopsy. The relationship between the sexes is interesting, inasmuch as the number of men and women approaches equality. The incidence of all aneurysms in males is five times that in the female. Garland, in 4,100 autopsies at the Massachusetts General Hospital, found only three aneurysms of the splenic

artery. Sperling, writing in 1940, found only three cases which had been diagnosed before operation or death. Lindboe, in 41,437 autopsies, reported 554 abdominal aneurysms, of which 26, or 0.05 per cent, were of the splenic artery. Anderson and Gray, writing in 1929, found 58 cases in the literature and reported an additional one. Machemer and Fuge, in 1939, found 24 additional cases in the ten years which had elapsed since the publication of the paper of Anderson and Gray. Schroeder, who wrote in 1918, reported 20 aneurysms of the splenic artery in a series of 32,768 autopsies. All reports indicate that the condition is a very rare one and that its coincidence with pregnancy is still more rare.

Published reports indicate that it is most frequent in the third decade, although the fourth, fifth, sixth, and seventh show nearly as many.

The cause cannot be stated too definitely. Binder says that syphilis, except in the case of aneurysm of the aorta, does not play a part. The study of the reported cases would indicate that calcification of the arterial wall, with attendant weakening, is of etiological importance. Ponfick suggests that endocarditis is as important etiologically and believes that an embolism at the point at which an artery branches in loose supporting tissue may be the determining force which produces the aneurysm.

Recognition of the condition is extremely difficult. Sperling suggests three suggestive signs which may help in determining the presence of a splenic aneurysm. These are: (1) left upper quadrant pain, (2) a systolic bruit over a palpable tumor mass, and (3) a pulsating filling defect in the greater curvature of the stomach as shown by the x-ray.

In the great majority of the reported cases diagnosis has not been made. It has been confused with cholelithiasis, cholecystitis, pancreatitis, and ectopic pregnancy. It may also simulate perforated gastric ulcer, mesenteric thrombosis, or a ruptured viscus. Two cases of successful preoperative diagnosis are reported by Höglér who found the pulsation of the mass by fluoroscopy.

In many of the reported cases, blood was found in the stool, and Lower and Farrell suggest the examination of the stool for undigested fat in order to detect a lessened pancreatic activity which may be due to the pressure of the mass upon the pancreas.

In the great majority of the reported cases, massive hemorrhage was found in the peritoneal cavity. In the first case here reported, in addition to an enormous retroperitoneal hematoma, there was a large amount of blood in the peritoneum. In some cases the hemorrhage did not terminate life at once. A primary hemorrhage took place, in many cases into the lesser peritoneal cavity. In the second case seen in this hospital, the patient remained in the institution fourteen days before death, which took place on the same day as the operation which was finally undertaken.

As to the prognosis, Lower and Farrell found that of 15 cases in the literature upon which operation had been done, 7 had recovered. If surgical therapy is to be attempted, it should be either the removal of the aneurysm, with the excision of the spleen as well, if necessary, or the ligation of the splenic artery. The latter procedure will carry with it an aseptic necrosis of the spleen which does no harm. The ligation of the splenic artery in experimental animals has

proved to be safe, and recovery has followed the ligation of the artery in human beings. In those cases in which tamponade was resorted to, death followed invariably.

In both the cases here reported and in that of Sered and Steiner, in both of which the patients were pregnant, death ensued. In the series of Baumgartner and Thomas, one case was found in which an aneurysm of the splenic artery ruptured during labor. The condition is evidently a most serious complication of pregnancy. It would seem that it is even more serious during pregnancy than at other times for two reasons. First, the difficulty of arriving at an accurate diagnosis at any time, even though the abdominal field may not be obscured by the large tumor incident to an advanced pregnancy. Second, the operative attack, without which the issue is nearly always fatal, is rendered far more difficult and dangerous by the presence of the pregnancy. In our own case, had it been possible to have recognized the presence of the aneurysm, after emptying the uterus by vaginal hysterotomy, we might have proceeded to deal with the aneurysm surgically. The condition of the patient at that time would have rendered the procedure hazardous, even without the preceding obstetric surgery. If the pregnancy is beyond the first four months, it would seem essential to do away with the uterine mass before attempting the upper abdominal surgery. Unless the cervix is easily accessible and not too long, the easiest way of doing this would be by abdominal section, preferably the low cervical type of hysterotomy. If the uterus could be emptied easily from below, it would have the advantage of avoiding two abdominal incisions.

In cases in which upper abdominal pain comes on suddenly without other obvious explanation, it is suggested that the possibility of aneurysm of the splenic artery be kept in mind. The triad of signs suggested by Sperling may be useful. If a palpable tumor is present, one should listen for a bruit, and the presence of a pulsating tumor, indicated by fluoroscopic examination of the stomach, may be very valuable. While the complication is a rare one, the fact that it is fatal, and that immediate recognition and efficient surgical attack may serve to rescue the patient, should cause the obstetrician to keep in mind the possibility, if not the probability, of such a condition and to recognize it if possible.

In the series of cases reported by Machemer and Fuge, are found eight in which the aneurysm was a complication of pregnancy. Their paper appeared in 1939. Since that time four additional cases have been reported to which the case noted herein may be added, making a total of 13 cases in the entire available literature since 1939. While the condition is not a common one, it occurs with sufficient frequency to make a familiarity with its symptoms desirable. Enough cases have occurred in pregnancy that it may well be kept in mind by the obstetrician when upper abdominal pain occurs, especially if accompanied by the signs of loss of blood.

Without active therapy, even in the absence of pregnancy, the prognosis is very poor. The outlook in general may be indicated by the analysis given by Machemer and Fuge. In 25 cases in which no surgical treatment was attempted, there were 18 deaths, a mortality of 75 per cent. In 13 cases in which surgical

treatment was tried, there were 7 deaths, a mortality of 47 per cent. In some of these cases the treatment was merely tamponade. In eight cases in which the aneurysm was removed, or in which the splenic artery was tied, there were two deaths, a mortality of 25 per cent. The numbers quoted are not sufficiently large to give a wholly accurate statistical picture but they strongly suggest that removal of the aneurysm or ligature of the artery is the best method of management. Tamponade is unsatisfactory and is accompanied by a high mortality.

References

- Wesenberg, W.: *Zentralbl. f. Gynäk.* 36: 463, 1912.
 Van Rooy, A. H. M. J.: *Nederl. Maandschr. v. Geneesk.* 14: 507, 1922.
 Lundwall, K., and Godl, A.: *Arch. f. Gynäk.* 113: 177, 1923.
 Saenger, H.: *Zentralbl. f. Gynäk.* 50: 1324, 1926.
 Mayer, E.: *Zentralbl. f. Gynäk.* 52: 754, 1928.
 Remmelts, R.: *Tijdschr. v. prakt. verlosk.* 33: 41, 1928.
 Sered, H., and Steiner, L. M.: *AM. J. OBST. & GYNEC.* 29: 606, 1935.
 Machemer, W. L., and Fuge, W. W.: *Arch. Surg.* 39: 190, 1939.
 Guy, C. C.: *Surgery* 5: 602, 1939.
 Sperling, L.: *Surgery* 8: 633, 1940.
 Lower, W. E., and Farrell, J. I.: *Arch. Surg.* 23: 182, 1931.
 Baumgartner, E. A., and Thomas, W. S.: *Surg., Gynec. & Obst.* 39: 462, 1924.
 Binder, V.: *Verhandl. d. deutsch path. Gesellsch.* 15: 221, 1913.
 Lindboe, E. F.: *Acta chir. Scandinav.* 72: 108, 1932.
 Schroeder, Carl: *Beitr. z. klin. Chir.* 111: 205, 1918.
 Anderson, W., and Gray, J.: *Brit. J. Surg.* 17: 267, 1929.
 Mayer, Elek: *Zentralbl. f. Gynäk.* 52: 754, 1928.
 Remizov, A. A.: *Soviet. khir.* No. 8, p. 126, 1935.
 Seids, J. V., and Hauser, H.: *Radiology* 36: 171, 1941.
 Kolb, O.: *Deutsche Ztschr. f. d. ges. gerichtl. Med.* 33: 254, 1940.
 Gillam, J. F. E.: *Brit. M. J.* 1: 69, 1942.
 Freitas, T. de: *Neurobiologia* 4: 230, 1941.
 Lennie, R. A., and Sheehan, H. L.: *J. Obst. & Gynaec. Brit. Emp.* 49: 426, 1942.
 Ponfick: *Virchow's Archiv.* 58: 528, 1873.
 Högler, F.: *Wien, Arch. f. inn. Med.* 1: 509, 1920.
 Gaveland, J.: *Boston M. & S. J.* 184: 385, 1921.

THE SEARCH FOR THE FEMALE SEX HORMONES

ROBERT T. FRANK, M.D., NEW YORK, N. Y.

HAVING taken part for more than twenty years in the search for and identification of the female sex hormones, I feel qualified in giving a vivid picture of this quite romantic chapter of endocrinology. Some of the functions of the gonads have been known since prehistory, as evidenced by the fact that castration was practiced on both the male and female of animal and human species. The knowledge that castration produced certain other changes, besides the abolition of the sex cycle, was accepted, as shown by history, both medical and lay. Yet as late as 1912, two prominent members of the American Gynecological Society did not hesitate to put themselves on record by stating boldly that, in their opinion, no proof has been given that the ovary had any function in addition to that of supplying ova.

In 1893, Regis, of Bordeaux, evidently influenced by Murray's success with thyroid substance, made a glycerin mash of animal ovaries and injected the mess subcutaneously into human beings afflicted with melancholia and other nervous diseases. He reported many striking successes. Actually, the distinct evidence of an internal secretory effect of the ovaries was first given simultaneously and independently by two Viennese workers: the one, Halban, an active and prominent gynecologist; the other, a laboratory man, Knauer, in 1898. They succeeded in re-establishing the sex cycle by reimplanting ovaries in rodents and monkeys. The next important milestone hails from Breslau. Ludwig Fraenkel, who is still active, now residing in Uruguay, in 1903 reported that removal of the corpus luteum invariably produced abortion in the pregnant rabbit. He had been led to undertake this research by his teacher, Borne, who died before completing his experiments. The so-called nidatory theory of the corpus luteum has been substantiated by all subsequent work. In 1905, Halban published an extremely important contribution, describing the internal secretory function of the placenta. His whole thesis was based on clinical observation. It covered the continuation of nidation, the breast changes, the uterine hyperplasia, and other symptoms associated with pregnancy. He based all of his conclusions on numerous clinical observations. In the years which have elapsed, all the experimental work and increase in knowledge has authenticated practically every point that he made. From 1908 on, working in Philadelphia, Leo Loeb undertook numerous carefully planned and well-controlled experiments on guinea pigs. By means of these he showed that the corpus luteum not only had the function ascribed to it by Fraenkel, of insuring the nidation of the ovum, but also that the corpus luteum controlled the periodicity of the sex cycle. Moreover, his experiments showed that the nidatory function was exerted through the production of a maternal portion of the placenta, both embryonal and maternal placenta being necessary for successful nidation and continuation of pregnancy.

It should be noted that during these preliminary years practically the entire attention of investigators was focused on the corpus luteum, which was considered the main, probably the sole, functional portion of the ovary. It is true that in 1906 the well-known physiologist, Starling, who had introduced the clear concept of "hormone," as observed in the production of gastric secretin, published a paper, with Lane-Claypon, on the factors which determine the growth and activity of the mammary gland. This paper, which postulated that the fetus and placenta contain a hormone which activated the breast, drew correct conclusions on entirely erroneous experimental data. The reason for their error was due to the fact that they were unaware of the breast changes occurring in the rabbit during the normal sex cycle. Unger and I drew attention to their error which, however, these distinguished investigators never acknowledged or conceded. It may be said that during this decade, inconclusive results were obtained with extracts of ovaries and placenta because practically all of the extracts used for experimental purposes were aqueous and, therefore, as our subsequent increase in knowledge has shown, failed to dissolve the lipoid soluble sex hormone. Consequently, the greatest advances were made by morphologic investigations throughout the cycle such as those of Leo Loeb. Another group of investigators who advanced our knowledge were the Frenchmen, Ancel and Bouin, who, from 1908 on, investigated the sex cycle, correlating ovarian and uterine, and mammary histological findings. They devised a method to produce what was then not yet known as "pseudopregnancy" in the rodent. They produced this by cohabitation with vasectomized males. The sex act caused the pseudopregnancy and therefore persistence of the corpus luteum. Investigations on human material threw additional light on the cycle. Hitschmann and Adler, Mayer, Albrecht and others correlated ovarian and uterine endometrial cycle by comparing specimens obtained at different intervals.

A new era of investigation dates from the time that an obscure instructor in chemistry in a French high school, Iscovesco, used various lipoid solvents in obtaining extracts from ovary, placenta, and various other organs. These extracts, which were fractionally separated by various nonmiscible solvents, produced very definite uterine changes in immature or castrated experimental animals. Throughout these researches which were extended by others, Herrmann in Vienna and also Fellner, Frank and Rosenbluth in New York, it was shown that corpus luteum extracts produced marked hyperplasia in the uterus of castrates. A variable reaction was obtained in the mucous membrane; sometimes there was marked glandular hyperplasia such as was noted by the morphologists in pseudopregnancy; sometimes this was absent. An explanation for this discrepancy was not discovered for many years.

In 1916 I came across an obscure observation of Bucura's, dating from 1908, which had attracted no attention whatever. In a resection of the ovaries of rabbits, in one case he found nothing but a single follicle which had developed, the rest of the ovary having been resected. He noted that the uterus of this animal at autopsy showed marked hyperplasia. This observation was buried in the literature for many years. Having worked with numerous associates in try-

ing to obtain a concentrate of the corpus luteum and to purify this, we reached a certain point, but, after that, further purification was unaccompanied by increased activity. Partly because I remembered Bucura's observation and partly because it seemed likely that the follicle fluid should have some function, in 1917 I obtained a considerable number of sow's ovaries, aspirated the fluid from the ripening follicles, and injected it into immature rabbits. A surprisingly rapid and marked hyperplasia of the uterus developed, not accompanied by an excessive arborization of the mucous membrane glands. Because of interruption produced by my entrance in the Armed Service and subsequent ill-health, I failed to publish this finding until 1922, although I had placed the record of it in care of the Crocker Cancer Research Laboratory in 1917. I published this observation in 1922 in the *Journal of the American Medical Association*. This was really the first definite proof offered that another constituent of the ovaries besides the corpus luteum produced a hormone. This concept was popularized and widely disseminated in 1923 by Allen and Doisy, who miscalled the follicle fluid the "ovarian hormone." Really, their main contribution at that time, a major one, was the rodent vaginal smear test as a qualitative test for estrogenic activity. As soon as this test became available, the slow, expensive, and tiresome test, based on gauging the size of the rabbit uterus, became obsolete, and speeding up the search for estrogens was immeasurably increased.

Even with the Allen and Doisy test available, the progress in isolating the active substance of the ovary did not gain greatly until Sigmund Loewe, previously of Dorpat, later in Frankfurt, discovered that great activity resided in the urine of pregnant women. Thus a solution of the hormone, let us call it by its present name of "estrogenic," in aqueous medium, eliminated the innumerable complicating contaminants present when the hormone was obtained from either ovarian or placental material. Doisy, and almost simultaneously Butenandt, isolated, crystallized, and determined the chemical structure of estrone. Within a surprisingly short time not only estrone but estriol and estradiol were isolated. The biochemists did an amazingly quick and thorough job so that today we know that the ovary produces the strongest hormone, estradiol, that during its metabolism it probably is reduced to estrone and estriol which have less activity, and is excreted in the form of compounds of glucuronic acid and sulfuric acid in the urine and feces. This is not the place to enter into details which are so readily available elsewhere.

In 1928, W. Allen and Corner went to work in purifying the corpus luteum extract, and gave clear-cut chemical evidence of the presence and activity of the corpus luteum and its effect upon the breasts and uterus. At this time they showed that the arborial glandular mucosal changes were corpus luteum in nature. They not only confirmed the work of the morphologists, Loeb, and Bouin and Ancel, etc., but they also gave a clear-cut experimental proof that the Borne-Fraenkel theory was a fact and that pregnancy after removal of the corpus luteum in ovaries could be continued by means of extracts containing progestin.

To date, the concluding chapter in the search for the sex hormones includes the discoveries by Philip E. Smith, and simultaneously and independently by

Aschheim and Zondek in 1926, that the anterior lobe of the pituitary contains the gonadotropic hormones which actually activate both the male and female gonad, proving that the gonads are, so to speak, stars of second magnitude. Whether these are one or two gonadotropic hormones, the one follicle stimulating, the other luteinizing, is still a moot question, and although considerable purification has been obtained, the integrally protein nature of these hormones has so far defied full identification.

In this very brief and summarized personal review, the innumerable building stones which were necessary for the construction of the entire picture could not be mentioned in detail. The first ten years of this century saw important but rather disconnected work performed, partly on animals, but largely histological in nature. The first half of the second decade was marked by research with crude extracts. It was not until the biochemists came to the aid of the gynecologists and physiologists that rapid and conclusive advances were made. There is still, however, much to be clarified in this fascinating subject.

1035 PARK AVENUE

THE ROLE OF PORRO CESAREAN SECTION IN MODERN OBSTETRICS

KARL M. WILSON, M.D., ROCHESTER, N. Y.

(From the Department of Obstetrics and Gynecology of the University of Rochester)

IT WAS in 1876 that Porro first removed the uterus following cesarean section. He did this in the hope of reducing the appalling mortality which was associated with the operation prior to the introduction of the Säger technique. The deaths associated with the old operation, when the uterus was not sutured, practically always resulted from hemorrhage or infection, and Porro sought to eliminate these factors by the removal of the uterus. While the immediate results were not brilliant as compared with modern-day surgery, they at least presented a definite improvement over those obtained with the old operation. Thus, in 1882, Godwin collected 134 cases with a maternal mortality of 55.8 per cent, a very high figure but still representing an improvement over the results previously obtained from the original operation.

Introduction of the Säger technique brought about further striking improvement in maternal results and also reduced materially the necessity for performing the Porro operation, which, after all, is a mutilating operation which permanently sterilizes the woman. While Porro's original technique of suturing the cervical stump to the lower angle of the abdominal incision is no longer followed, but rather a subtotal or total hysterectomy by modern surgical methods is done, yet his name is still attached to the procedure and such an operation is generally spoken of as a Porro cesarean section.

Although the introduction of the Säger technique, together with the application of, first antiseptic and, later, aseptic measures, reduced the cesarean section mortality very materially, the results still left a good deal to be desired. This was due largely to the fact that a long time elapsed before it was recognized that the classical cesarean section is a dangerous procedure if not done before labor sets in or at the very onset of labor. Introduction of the technique of the lower cervical cesarean section and the various forms of extraperitoneal operations, however, today permit reasonably safe abdominal delivery for many women whose lives would be jeopardized by performing the classical operation. These techniques have also reduced materially the necessity for performing the radical operation.

While this is true, it is also a fact, however, that, on occasion, removal of the uterus after cesarean section will be very definitely indicated. Indicative of the decreased frequency for the necessity of this operation, comparison may be made between a series from the clinic of the late J. Whitridge Williams, reported by Harris in 1922, and the series presented herewith. In the former series of 223 cesarean sections the uterus was removed in 64 instances, or 29.5 per cent, while in our series of 355 cesarean sections of various types it has been found necessary to remove the uterus only 31 times, an incidence of 8.7 per cent.

The indications for this operation are relatively few but they are of great importance. In the present series there were four particular indications for which the operation was done: namely, myomas of the uterus, uncontrollable hemorrhage, severe intrapartum infection, and in order to effect sterilization.

Record of Cases at Strong Memorial Hospital

Myomas of the Uterus.—In ten women the uterus contained myomas of such a size and in such position as to demand delivery by cesarean section. At the time of operation the myomas were found to be of such size or so numerous as to preclude myomectomy, so the uterus was removed. All made excellent recoveries and the infants all survived (one case of twins). It is interesting to note that six of the women were elderly primiparas—over 35 years of age. In each instance the operation was done as an elective procedure and before the onset of labor.

Uncontrollable Hemorrhage.—In seven women it was found necessary to remove the uterus after cesarean section on account of this indication. In five of these women the cesarean section was done on the indication of abruptio placentae, and following the emptying of the uterus, as often happens in such hemorrhagic and infiltrated uteri, bleeding continued to a degree to endanger seriously the patient's life and could not be controlled by the usual measures. Under the circumstances, nothing remained to be done except to remove the uterus in order to avoid a tragedy.

Differences of opinion exist as to the best method for the treatment of acute premature separation of the placenta with concealed hemorrhage, but one of the advantages offered by delivery by cesarean section is the opportunity to observe the uterus, its condition and its behavior after emptying, preserving it when possible, but removing it without hesitation if bleeding cannot be controlled.

In two other women on whom classical elective cesarean sections were done, one on a young woman for contracted pelvis, the other on an elderly primipara of 42 years, uncontrollable bleeding occurred after delivering the child and placenta, so that it was necessary to sacrifice the uterus in these two women—a tragic circumstance in the young woman but not of such great significance in the older woman. It is interesting to note that in these two operations removal of the uterus was deferred to the last possible minute; in fact, in both instances the uterine incision had been sutured before it was recognized that removal of these uteri was demanded on account of their complete failure to contract. From one of these, after removal, 1,000 c.c. of blood were collected from the cavity. This represents a difficult situation, requiring a quick decision but at the same time the greatest nicety of judgment. In the uterus not damaged by hemorrhagic infiltration, as in abruptio placentae, the problem of uncontrollable hemorrhage is fortunately encountered very infrequently. In this group all the women made excellent recoveries, but five infants were stillborn. These stillbirths occurred in the five women presenting abruptio placentae, the infants being dead at the time the operation was begun.

Intrapartum Infection.—In nine women the uterus was removed following cesarean section on account of the existence of a severe intrapartum infection at the time the operation was done. This is the type of case in which the operation was formerly most frequently employed, and is also the group in which modern methods of obstetric practice should materially reduce the necessity for the operation. Fewer neglected cases are seen than formerly, and proper resort to lower cervical and extraperitoneal section in suitably selected cases should also reduce the necessity for resort to the more radical operation.

In reviewing this particular group of nine women, it would appear that three of them might possibly have been delivered with reasonable safety by some form of extraperitoneal cesarean section. These are to be regarded as potentially infected rather than frankly infected. The others, however, had had various types of manipulation from below before the operation was done and presented frank evidence of intrapartum infection of a serious nature.

Even with the advent of the sulfonamides and penicillin, admittedly valuable and forceful agents for combating infection, it would seem to me an undue risk to leave the frankly infected uterus in situ after cesarean section.

In this group all the women recovered, but one developed a wound infection which necessitated a secondary closure.

There were four stillbirths or neonatal deaths, two from atelectasis, one double monster on which evisceration had been attempted before operation, and one in connection with a placenta previa, the infant being dead at the time of operation.

Sterilization.—In five women the uterus was removed as a means of effecting sterilization at the time cesarean section was done for other reasons. This is not the usual method for effecting sterilization nor, on the whole, is it the most desirable. On the other hand, it is possible on occasion to obtain permission for hysterectomy when permission for resection of the tubes would be refused. Also, on occasion, menstrual disturbances prior to the pregnancy may warrant removal of the uterus, or the patient may request it.

All five of these women made good recoveries, but one baby failed to survive, due to prematurity. This neonatal death occurred in the case of a woman previously delivered by cesarean section, the operation being followed by a serious infection. On admission, she had a deeply furrowed uterus which impressed us as being unable to withstand further distention although the baby was as yet obviously small. Sterilization, by removal of the uterus, was at her request. The child weighed only 1,200 grams and died in twenty-four hours.

TABLE I. SUMMARY OF CASES

INDICATION	NO. OF CASES	MATERNAL DEATHS	FETAL DEATHS
Myoma uteri	10	0	0
Uncontrollable hemorrhage	7	0	5
Intrapartum infection	9	0	4
Sterilization	5	0	1
Total	31	0	10 or 32.2%

Summary and Conclusions

A series of 31 women in whom cesarean section followed by supravaginal amputation of the uterus (Porro cesarean section) was performed is presented. The maternal results were uniformly good, there being no maternal deaths. That, of course, is not to say that the operation is without mortality, as the series is a small one. There were 10, or 32.2 per cent, stillbirths or neonatal deaths. None of them can be attributed to the operation, as in seven instances the infant was known to be dead at the time the operation was done and had died as the result of the condition for which cesarean section was indicated. Two mature infants died of atelectasis and one infant of prematurity.

This operative procedure still has an important place in obstetric operative procedures, though the necessity for it has decreased materially following the introduction of other operative techniques, such as the low cervical cesarean section and the various forms of extraperitoneal operations. Also, with improved prenatal care and increasing hospitalization of obstetric patients, fewer neglected cases are seen.

The particular indications for removal of the uterus after cesarean section are found to be: (a) Myomatous uteri containing myomas of such a size and in such a position as to necessitate cesarean section in the first place, and when

myomectomy is precluded. (b) Uncontrollable hemorrhage when removal of the uterus is necessary as an emergency lifesaving measure, often in association with abruptio placentae but occasionally encountered apart from this. (c) The presence of frank intrapartum infection when cesarean section is done. It is in this group in particular that a decrease in the necessity for the removal of the uterus has occurred, and further reduction should be possible. (d) As a means of effecting sterilization when sterilization is indicated and where for some reason it may seem preferable to remove the uterus rather than to resect the tubes.

No examples of ruptured uterus requiring hysterectomy are included in this series as this would seem to be an entirely separate problem.

ECTOPIC GESTATION

The Diagnostic Value of Cul-de-sac Aspiration

LUCIUS E. BURCH, M.D., F.A.C.S., AND JOSEPH SEITCHIK, M.D.,
NASHVILLE, TENN.

ECTOPIC gestation or extrauterine pregnancy is more often overlooked and more often diagnosed when not present, than any other serious pelvic lesion.¹ Farrell and Scheffey² of Jefferson Medical College reported 157 cases of ectopic gestation from Sept. 21, 1921, to Sept. 1, 1942. A correct diagnosis was made in 76 per cent of the cases. Child and Douglas³ reported three normal pregnancies and three incomplete abortions diagnosed as ectopic pregnancies. Torpin⁴ recently reviewed the literature and showed an incorrect diagnosis ranging from 14.8 per cent to 47 per cent from fourteen different clinics with an average of 27.3 per cent incorrect. These reports from the best clinics in the country clearly show how difficult it is to make a correct diagnosis.

We have divided ectopic gestation into two varieties—the typical and the atypical; the typical comprises 40 per cent of the cases, the atypical 60 per cent. The history of the case, symptoms, and physical signs stand out first in importance in making a diagnosis. It is a disease that occurs only during the sexual life of the woman. It is most common between 20 and 30 years of age. Next in frequency is the fourth decade. A small percentage of cases is found below 20 and above 40 years of age.

A preceding history of sterility before the occurrence of an ectopic gestation is quite common. It is usually found in women of low fertility. A history of pelvic inflammatory disease, infection following labor or abortion, or an infection following abdominal section for a ruptured appendix is quite common. The Vanderbilt cases showed pain present in 100 per cent; a missed period in 90 per cent; a bloody vaginal discharge in 89 per cent, and a mass in the pelvis in the typical variety in less than 50 per cent and present in the atypical in over 90 per cent.

The typical case is characterized by a violent pain in the abdomen associated with a bloody vaginal discharge and shock. Usually there is a history of a missed period. Shoulder pain is present in 25 per cent of the cases and is a most valuable symptom. Rigidity of the abdominal muscles is generally absent, but tenderness on palpation, either general or localized, is present in the lower quadrant.

On vaginal examination we note a pelvic mass is absent in about 55 per cent of the cases. A mass may be palpated if the free blood present has formed clots or if the pregnancy is sufficiently large to be palpated. If sufficient blood has

been lost, there will be a decrease in the hemoglobin and red blood cells which, in many cases, is quite marked. The white blood count rarely goes above 15,000, although in the massive hemorrhage this may go to 20,000 which decreases as the blood is absorbed. The pulse rate is accelerated and the temperature is subnormal. Preparation should be made for operation and blood should be administered to bring these patients out of shock while the operating room is being prepared. The transfusion needle should be left in place in order to give more blood during or after the operation. In those institutions in remote areas that do not maintain a blood bank or have plasma available or in those cases in which there is an Rh factor or an unusual type of blood, we would suggest autotransfusion, or reinfusion of the patient's own blood.

In 1923 I reviewed the literature on autotransfusion, and strongly advise the use of this procedure.⁶ We cannot be too emphatic in urging in the typical case a quick diagnosis and an early operation.

In the atypical variety the patient is not in shock. The sighing respiration and the blanched appearance are absent. The thready pulse and the subnormal temperature are not present. It is in this variety that time can be taken to make use of procedures so useful in arriving at a correct diagnosis.

We have reviewed the cases of ectopic gestation in the Vanderbilt University Hospital from Sept. 1, 1925, to July 1, 1945. This study comprises an analysis of 105 patients who were admitted or discharged with the diagnosis of ectopic gestation. Sixteen patients were admitted with a diagnosis other than ectopic gestation, but extrauterine pregnancies were found at operation. Eighteen patients were admitted in shock. Seventeen of these had extrauterine pregnancy. The other patient had a ruptured corpus luteum with intraperitoneal hemorrhage. The remaining 71 patients were admitted with a suspected diagnosis of ectopic pregnancy.

The common conditions in which a mistaken diagnosis is often made are: pelvic inflammatory disease, abortion, a cyst of the corpus luteum producing a positive Aschheim-Zondek test, a normal pregnancy associated with a large corpus luteum, a small ovarian cyst which is inflamed and associated with torsion of the pedicle, a ruptured Graafian follicle or corpus luteum producing an intraperitoneal hemorrhage with shock, a normal pregnancy with a soft uterine wall with an extreme dextrorotation, and abdominal pregnancies. A mistaken diagnosis may also be made of the following: pregnancy in the uterus associated with a tubal pregnancy, pregnancy in a bicornate uterus, tubal pregnancy associated with a cyst in a case which had formerly had one tube removed for ectopic gestation. The discovery during operation of ectopic gestation for the mistaken diagnosis of appendicitis is not an unusual mistake. Pregnancy tests are of value but a diagnosis should not be dependent on this test. There are many conditions which will produce a positive pregnancy test when pregnancy is not present. The most common ones are: chorioepithelioma, hydatidiform mole, missed abortion, teratoma of testicles, embryonal adenocarcinoma, seminoma, myosarcoma, teratoma of ovary, luteum cyst, granulosa-cell carcinoma, para-ovarian cyst, and certain forms of psychosis.

We might add that any case which is diagnosed as appendicitis is entitled to a pelvic or rectal examination and a careful review of the menstrual cycle before operation.

In pelvic inflammatory disease, pain usually makes its appearance at the time of the period or just after it. The history of the case, signs of gonorrheal infection, smears, culture, sedimentation rate, and leucocyte count are of value, but at times deceptive. In gonorrhea the leucocyte count will run between 15,000 and 20,000. In ectopic gestation it is usually below 15,000. The temperature in ectopic is rarely above 102° F. In pelvic inflammatory disease it may run as high as 103° F. The sedimentation rate is more rapid than in ectopic. The pregnancy test is often positive in ectopic and in gonorrhea it is negative. Gonorrheal salpingitis produces a bilateral adnexal mass with an associated lower abdominal rigidity, whereas ectopic produces a unilateral mass and the rigidity, if present, is on the affected side. In gonorrhea the pain is constant; in ectopic it is intermittent. Culture for gonococci is a laboratory procedure of great value and should always be used in a suspected case. The finding of blood in the peritoneum should clear up the diagnosis.

Abortion is easily mistaken for ectopic gestation. Curettage may assist in the diagnosis by finding chorionic villi or decidual membranes in the scrapings. Some advise its use as a routine measure and as an aid in the diagnosis of the atypical case. We do not concur in this view and believe a curettage for diagnostic purposes in a case of partial rupture or tubal abortion may bring on an intraperitoneal hemorrhage with possibly a fatal result. When one has a suspected case of abortion, ectopic should be ruled out; and in suspected cases of ectopic, abortion must be eliminated.

Cullen's sign or blue navel indicates an intraperitoneal hemorrhage. It is rarely found.

Israel⁵ reported six cases of corpus luteum cyst and in two of these a positive pregnancy test was present. In the Vanderbilt series one case of corpus luteum cyst with a positive pregnancy test was found.

A ruptured Graafian follicle usually occurs at the midmenstrual interval. A ruptured corpus luteum occurs just before the onset of menstruation. A most confusing condition is a normal pregnancy associated with a soft uterine wall and an extreme dextrorotation. We recently had a case of this kind associated with a small fibroid the shape and size of the uterus in the pelvis. A mistaken diagnosis was made from the impression that the fibroid was the uterus and the dextrorotation of the normal pregnancy was either a cyst with torsion or perhaps an ectopic gestation. One pregnancy test in this case was positive, the other was negative. This unpardonable error would not have occurred if a pneumoperitoneum had been carried out, followed by x-ray.

South American surgeons have advised the use of an opaque substance injected in the uterus followed by an x-ray picture. They claim that this injection will not dislodge a pregnancy in the tube and that it will clearly show a pregnancy if present. We would not advise this procedure until time and further experience show it to be free of danger. We have found the injection

of carbon dioxide gas into the peritoneum through an abdominal puncture followed by an x-ray of the pelvis a procedure of great value in arriving at a diagnosis. It is free of danger but can be used only in those institutions where there is a close cooperation with the x-ray department which is trained in this technique. The peritoneoscope is an instrument which has a great future. It must be used by a man who has had experience and training. We gave up the use of this instrument during the war, due to rapid changes in the staff and the inability to assign one man to this particular duty.

We desire to emphasize especially in this paper the value of aspiration of the peritoneum either per vaginam or through the abdominal wall if conditions in the cul-de-sac make it not advisable to aspirate per vaginam. It is not an original procedure. It is one that we have used not only in making a correct diagnosis, but also in avoiding unnecessary operations. The procedure is not time consuming and can be used in any institution or hospital or even in the private home if necessary. If the aspirated blood shows an absence of rouleaux formation and the erythrocytes show a crenated appearance, it signifies a hemorrhage into the peritoneal cavity.⁷

In obtaining blood from the peritoneal cavity we look for color, viscosity, presence of small clots, and clotting time. The old blood has a definite brownish tint. It is thinner than fresh blood and does not clot. We have usually used a size 17 needle, which is large enough to permit the aspiration of small clots.

Review of Cases

Of the 71 suspected cases of ectopic gestation admitted in good condition and presenting diagnostic difficulty (Table II), 42 patients, or 62 per cent, were found to have extrauterine pregnancies. Twenty-nine patients did not have ectopic pregnancies, but had some other difficulty summarized in Table I.

TABLE I

Corpus luteum cyst	6
Pelvic inflammatory disease including all diagnoses such as pelvic abscess, salpingitis, tubo-ovarian abscess, pyosalpinx, etc.	15
Follicle cysts	2
Undiagnosed	5
Metastatic adenocarcinoma of the cul-de-sac	1
	<hr/> 29

In 22 patients, puncture was performed (this includes two cases of abdominal puncture) and old blood was obtained. Twenty of these cases had extrauterine pregnancies, one had a ruptured follicle cyst with marked intraperitoneal bleeding, and one had an adenocarcinoma of the cul-de-sac. This gives us a diagnosis rate of 91 per cent. Of the fifteen cases that had cul-de-sac puncture, but no old blood was obtained, none were proved to be ectopic pregnancies. While it is always possible that some of them might represent tubal abortions, the fact remains that when laparotomies were performed on five of them, no ectopic was found. The remaining 34 cases were not subjected to cul-de-sac puncture and in 12 of them no ectopic gestation was found. To summarize: if we consider the presence of old blood obtained by cul-de-sac puncture a positive test for ectopic gestation,

and if we consider the absence of old blood as a negative test, we may say that in this series of 37 patients exposed to cul-de-sac puncture, there were no false negative tests and two false positive tests. In our hands, the cul-de-sac puncture when used as a test for the presence or absence of extrauterine pregnancy is accurate in 94.6 per cent of the cases. This compares very favorably with the correct diagnosis rate of 65 per cent for 34 cases that were diagnosed only by the usual clinical and laboratory means.

TABLE II

	NUMBER OF CASES	NUMBER CORRECTLY DIAGNOSED	NUMBER INCORRECT DIAGNOSIS	% CORRECT DIAGNOSIS
Cul-de-sac puncture and old blood obtained	22	20	2	91
Cul-de-sac puncture and no old blood obtained	15	15	0	100
No cul-de-sac puncture	34	22	12	65
Total	71	57	14	80.3

TABLE III

	NUMBER OF LAPAR- OTOMIES	UNNECES- SARY LAPAR- OTOMIES	NECESSARY LAPAROT- OMIES	% OF UN- NECESSARY LAPAROT- OMIES
Cul-de-sac puncture performed and old blood obtained	21	0	21	0
Cul-de-sac puncture performed and no old blood obtained	5	5	0	100
No cul-de-sac puncture performed	33	10	23	30
Total	59	15	44	25

Table III is most interesting. We have attempted to analyze the 71 cases to determine how many unnecessary surgical operations were performed because of a suspected diagnosis of ectopic gestation. An unnecessary laparotomy is defined as one performed for some pelvic pathology for which we would not have operated had a true diagnosis been known preoperatively. Twenty-one of these cases were operated on after a cul-de-sac puncture and in this group of patients no unnecessary surgical procedures were performed. In five cases in which no old blood was obtained, the surgeon ignored the cul-de-sac puncture and laparotomy was performed. In no case was any pathology worthy of surgery found. Thirty per cent of these operations without cul-de-sac puncture were unnecessary. We believe that the presence of old blood obtained by a cul-de-sac puncture is an absolute indication for surgery. The absence of old blood so obtained is a contraindication to surgery performed because of the suspected presence of an extrauterine gestation.

Howard Kelly many years ago advised colpotomy. It is a valuable procedure as an aid in making a diagnosis, but why carry out a major surgical procedure to obtain information that can be easily obtained by an aspiration per vaginam or through the abdominal wall. We consider aspiration the most valuable of all aids in making a diagnosis of doubtful cases of ectopic gestation. Next to aspiration we consider pneumoperitoneum and x-ray as a valuable aid.

All of us make mistakes. All of us occasionally do an unnecessary operation. We are of the opinion, however, that with a careful study of this most

interesting and sometimes fatal condition, giving due consideration to the history, the physical signs, the laboratory tests, x-ray, and especially aspiration, our margin of error will be greatly reduced.

References

1. Curtis: Textbook of Gynecology, ed. 4, Philadelphia, 1942, W. B. Saunders Co., p. 538.
2. Farell, D. M., and Scheffey, L. C.: AM. J. OBST. & GYNEC. 46: 686, 1943.
3. Child, C. G., and Douglas, R. G.: AM. J. OBST. & GYNEC. 47: 213, 1944.
4. Torpin, Richard: South. M. J. 38: 485, 1945.
5. Israel, S. L.: AM. J. OBST. & GYNEC. 44: 22, 1942.
6. Burch, Lucius E.: Surg., Gynec. & Obst. 36: 511, 1923.
7. Kulen, Kamph: Zentralbl. f. Gynäk. 65: 379, 1941.

INDEX TO VOLUME 50

AUTHORS INDEX*

A

- AABERG, MONRAD, AND ROBY, CHARLES, Erythroblastosis fetalis in twin pregnancy, 548
- ABARBANEL, A. R., AND LEATHEM, J. H., Studies in amenorrhea, oligomenorrhea, and anovulomenorrhea. I. Effect of equine gonadotrophin upon establishment of cyclic menses and ovulation, 262
- ABRAMS, RUTH D., Social service and cancer, 571 (Special article)
- ADAIR, FRED L., Government and maternal welfare, 713
- (WITH HAC, LUCILE R., HESSELTINE, H. CLOSE, AND CRUDIM, MYRTLE B.), Sulfonamide and stilbestrol therapy in gonococcal vulvovaginitis, 88
- (WITH WATTS, RUTH M.), A transplantable rat tumor, 11
- ALTER, NICHOLAS M. (WITH NORTON, JAMES F.), Primary ovarian pregnancy, 535
- ANDROS, GEORGE J., Blood pressure in normal pregnancy, 300
- , AND HENDERSON, CHARLES W., Experience with continuous caudal analgesia in obstetrics at the University of Michigan Hospital, 68
- (WITH NEWTON, CHARLES W., JR.), Continuous caudal analgesia in curettage for abortion, 430
- ANGELUCCI, HELEN M., The treatment of trichomonas vaginitis with a sulfonamide compound, 336
- ANSPACH, BROOKE M., A review of the problem of cancer of the cervix since the use of radium in 1912, 681
- AYRE, J. ERNEST, BAULD, W. A. G., AND KEARNS, P. J., Primary carcinoma of the Fallopian tube, 196
- , —, AND —, Test case to show value of cervical cytology smear in uterine cancer diagnosis, 102

B

- BABA, GEORGE (WITH SCHMITZ, HERBERT E.), Aquinone during labor; its effect on the prothrombin level of the newborn infant, 292
- BALLINA, J. B., AND CHIODI, N. E., Ovarian pregnancy, 456
- BAPTISTI, ARTHUR, JR., Five years' experience with caudal anesthesia in private obstetric practice, 180
- BARNUM, CHARLES G., Dystocia due to the shoulders, 439
- BAULD, W. A. G. (WITH AYRE, J. ERNEST, AND KEARNS, P. J.), Primary carcinoma of the Fallopian tube, 196
- (WITH AYRE, J. ERNEST, AND KEARNS, P. J.), Test case to show value of cervical cytology smear in uterine cancer diagnosis, 102
- BEILLY, JACOB S., AND KURLAND, IRVING I., Relationship of maternal weight gain and weight of newborn infant, 202
- BERMAN, WILLIAM, Congenital absence of the sacrum and coccyx complicating pregnancy, 447

- BISHOP, EDWARD H. (WITH MOHLER, ROY W.), Complete abdominal hysterectomy, 489
- BLINICK, GEORGE (WITH FALK, HENRY C.), Pathogenesis of postabortal peritonitis, 168
- BOURGEOIS, GEORGE A., A peritoneal staining technique for extraperitoneal cesarean section, 191
- BOURLAND, J. W. (WITH MENGERT, WILLIAM F.), The circulation of amniotic fluid, 79
- BOWMAN, DONALD E., Reducing properties of the chorionic gonadotropic hormone as related to the chemical determination of pregnancy, 218
- BOYERS, L. MORGAN (WITH PAGE, ERNEST W.), Coccidioidal pelvic inflammatory disease, 212
- BOYS, CHARLES E., Strangulated hernia containing pregnant uterus at term, 450
- BRADY, LEO, AND REID, ROGER D., Lactobacillus therapy in vaginitis due to trichomonas, 509
- BROSNAN, JAMES T. (WITH FALLON, JOHN, AND WHELAN, CHARLES F.), Differential stethoscope for determining patency of each tube, 568
- BROWNE, O'DONEL, The Dublin Lying-In (Rotunda) Hospital bicentenary (1745-1945), 578 (Special article)
- BURCH, LUCIUS E., AND SEITCHIK, JOSEPH, Ectopic gestation, 765

C

- CHARVET, L. (WITH TRAUT, H. F., MCIVOR, B. C., HOWARD, J., AND LUCIA, S. P.), The Rh factor in obstetrics, 722
- CHESLEY, LEON, AND WILLIAMS, LAURA O., Renal glomerular and tubular function in relation to the hyperuricemia of pre-eclampsia and eclampsia, 357
- CHIODI, N. E. (WITH BALLINA, J. B.), Ovarian pregnancy, 456
- CHRISTIE, FRANK G. S., Myxosarcoma of vagina associated with early pregnancy, 553
- CHRISTY, CHRIST J., Vitamin E in menopause. Preliminary report of experimental and clinical study, 84
- COLLINS, JAMES (WITH MILLER, NORMAN F., AND WILLSON, J. ROBERT), The surgical correction of congenital aplasia of the vagina, 735
- CRAIG, IRWIN T., AND SCHENK, K. W., Uterus didelphys complicating pregnancy, 556
- CRUDIM, MYRTLE B. (WITH HAC, LUCILE R., HESSELTINE, H. CLOSE, AND ADAIR, FRED L.), Sulfonamide and stilbestrol therapy in gonococcal vulvovaginitis, 88
- CURTIS, ARTHUR H., Hypertrophy of uterus, 748

D

- DANFORTH, W. C., Aneurysm of the splenic artery with rupture. A rare complication of pregnancy, 753
- , Vaginal hysterectomy in the management of descensus uteri, 376

*July, pp. 1-118; August, pp. 119-234; September, pp. 235-352; October, pp. 353-470; November, pp. 471-594; December, pp. 595-770.

- DAUGHTRY, DEWITT C., Arrhenoblastoma, 539
- DAVIS, C. D. (WITH HAMBLIN, E. C.), Treatment of hypoovarianism by the sequential and cyclic administration of equine and chorionic gonadotropins—so-called one-two cyclic gonadotropic therapy, 137
- , AND HAMBLIN, E. C., A comparative study of the clinical responses of women with hypofunctioning ovaries to two methods of combined gonadotropic therapy, 269
- DAVIS, CARL HENRY, Gonorrheal arthritis complicating pregnancy treated with penicillin, 215
- DECKER, ALBERT, A simple technique to test tubal patency, 227
- DIECKMANN, WILLIAM J., Cesarean section mortality, 28
- , TURNER, DOROTHEA F., AND RUBY, BARBARA A., Diet regulation and controlled weight in pregnancy, 701
- DILEONE, RALPH (WITH WATERMAN, GEORGE W.), Treatment of carcinoma of the cervix by interstitial radium needles at the Rhode Island Hospital, 482
- DOUGLASS, LOUIS H. (WITH MORRISON, J. HUFF), Rupture of the uterus, 330
- DOWNING, WENDELL, AND O'TOOLE, LAWRENCE, Parovarian cyst causing dystocia, 106
- DRESSER, RICHARD (WITH SMITH, GEORGE VAN S.), Carcinoma of the uterine cervix. Interval report on treatment, results, and complications, 1
- DUBIN, ALVIN (WITH HALPERIN, JACOB, AND JACOBI, MENDEL), The Rh factor in obstetrics, 326

E

- ELDEN, C. A., Passage of a catheter through the uterus into the abdominal cavity, 569
- ELLER, WILLIAM C., AND RANDALL, JOHN H., Nausea of pregnancy treated by forced hydration, 518

F

- FALK, HENRY C., AND BLINICK, GEORGE, Pathogenesis of postabortal peritonitis. A study of 61 cases, 168
- FALLON, JOHN, BROSNAN, JAMES T., AND WHELAN, CHARLES F., Differential stethoscope for determining patency of each tube, 568
- FAULKNER, ROBERT L., AND RIEMENSCHNEIDER, E. A., Reactivation of endometriosis by stilbestrol therapy, 560
- FINEGOLD, WILFRED J., AND SCHUSTER, EUGENE B., Avulsion defects of the scalp of the newborn infant. Medicolegal implications, 108
- FRANK, ROBERT T., Heminecrosis of cervical stump following supravaginal hysterectomy, 226
- , Intraperitoneal nabothian cyst, 107
- , The search for the female sex hormones, 757

G

- GAMBLE, THOMAS O., MILLER, LLOYD C., AND TAINTER, M. L., Benzyl penicillin—clinical toxicity and efficacy by mouth in impetigo in the newborn infant, 514
- GRAFF, ADA M. (WITH MANDEL, HOWARD STEPHEN, AND GRAFF, SAMUEL), Placental senescence and the onset of labor, 471
- GRAFF, SAMUEL (WITH MANDEL, HOWARD STEPHEN, AND GRAFF, ADA M.), Placental senescence and the onset of labor, 471
- GREELEY, ARTHUR V. (WITH WILLIAMSON, HERVEY C.), Management of placenta previa, 398
- GREENBERG, EMANUEL, On a nonclotting component of postpartum blood, 532
- GREENE, GEORGE G., A seven-year review of eclampsia with special reference to treatment with veratrum viride, 427

- GROSSMANN, LAWRENCE L., The treatment of primary dysmenorrhea with deproteinized pancreatic extract (depropaex), 411
- GUSBERG, S. B., Androgen therapy of menopausal symptoms in cancer patients, 502
- GUTERMAN, HENRY S. (WITH RUBENSTEIN, B. B.), A simple technique for preparing vaginal smears, 565

H

- HAAS, R. L., Should we change our present standard of infant viability? 406
- HAC, LUCILE R., HESSELTINE, H. CLOSE, ADAIR, FRED L., AND CRUDIN, MYRTLE B., Sulfonamide and stilbestrol therapy in gonococcal vulvovaginitis, 88
- HALPERIN, JACOB, JACOBI, MENDEL, AND DUBIN, ALVIN, The Rh factor in obstetrics, 326
- (WITH DAVIS, C. D.), A comparative study of the clinical responses of women with hypofunctioning ovaries to two methods of combined gonadotropic therapy, 269
- , AND DAVIS, C. D., Treatment of hypoovarianism by the sequential and cyclic administration of equine and chorionic gonadotropins—so-called one-two cyclic gonadotropic therapy, 137
- HANLEY, BERNARD J., AND MALONE, CHARLES M., Caudal analgesia in obstetrics with special reference to repeated single blocks, 306
- HARDING, FLOYD E., The treatment of functional dysmenorrhea with pregnenolone, 56
- HAWKINS, M. C., JR., Pregnancy in a diverticulum from the uterus, 562
- HENDERSON, CHARLES W. (WITH ANDROS, GEORGE J.), Experience with continuous caudal analgesia in obstetrics at the University of Michigan Hospital, 68
- HESSELTINE, H. CLOSE (WITH HAC, LUCILE R., ADAIR, FRED L., AND CRUDIN, MYRTLE B.), Sulfonamide and stilbestrol therapy in gonococcal vulvovaginitis, 88
- HOWARD, J. (WITH TRAUT, H. F., MCIVOR, B. C., LUCIA, S. P., AND CHARVET, L.), The Rh factor in obstetrics, 722
- HUDSON, GWEN S., AND RUCKER, M. PIERCE, Gas bacillus infection of the uterus treated with penicillin, 452

I

- INGRAM, C. H., JR., Therapy in habitual abortion, 154
- IRVING, FREDERICK C., Ten years of cesarean section at the Boston Lying-In Hospital, 660

J

- JACOBI, MENDEL (WITH HALPERIN, JACOB, AND DUBIN, ALVIN), The Rh factor in obstetrics, 326
- JOHNSON, HERMAN W., The conservative management of some varieties of placenta previa, 248
- JONES, G. E. SEEGAR, AND TE LINDE, R. W., The curability of granular-cell tumors, 691

K

- KAPLAN, IRA I., The effect of irradiation on the function of the ovary in young girls, 340
- KEARNS, P. J. (WITH AYRE, J. ERNEST, AND BAULD, W. A. G.), Primary carcinoma of the Fallopian tube, 196
- (WITH AYRE, J. ERNEST, AND BAULD, W. A. G.), Test case to show value of cervical cytology smear in uterine cancer diagnosis, 102

- KURLAND, IRVING I. (WITH BEILLY, JACOB S.), Relationship of maternal weight gain and weight of newborn infant, 202
- KUSHNER, J. IRVING, AND POSNER, A. CHARLES, Craniotomy, with review of cases, 95

L

- LASH, A. F., Hypernephroid carcinoma of the kidney of adrenal (?) and pregnancy, 221
- , Teratoma of the perineum in a newborn infant, 344
- LEATHEN, J. H. (WITH ABARBANEL, A. R.), Studies in amenorrhea, oligomenorrhea, and anovulomenorrhea. I. Effect of equine gonadotrophin establishment of cyclic menses and ovulation, 262
- LEDDEN, LEWIS J. (WITH NICODEMUS, ROY E., AND RITMILLER, LEROY F.), Continuous caudal analgesia in obstetrics and gynecology, 312
- LESH, RUTH ELLIS, Mesenteric thrombosis complicated by dermoid cyst, 422
- LEVINE, WILLIAM, Cesarean section under fractional spinal anesthesia, 75
- LIM, KHA TI, AND SNYDER, FRANKLIN F., The effect of respiratory stimulants in the newborn infant, 146
- LUCIA, S. P. (WITH TRAUT, H. F., MCIVOR, B. C., HOWARD, J., AND CHARVET, L.), The Rh factor in obstetrics, 722

M

- MCIVOR, B. C. (WITH TRAUT, H. F., HOWARD, J., LUCIA, S. P., AND CHARVET, L.), The Rh factor in obstetrics, 722
- MCLANE, CHARLES M., The isometric method of x-ray pelvimetry as a routine procedure, 495
- MCLENNAN, CHAS. E., Results of various types of treatment in adenocarcinoma of the endometrium, 254
- MALONE, CHARLES M. (WITH HANLEY, BERNARD J.), Caudal analgesia in obstetrics with special reference to repeated single blocks, 306
- MANDEL, HOWARD STEPHEN, GRAFF, SAMUEL, AND GRAFF, ADA M., Placental senescence and the onset of labor, 471
- MARCHETTI, ANDREW A., Catharina Geertruida Schraders and her diary. A note on the history of obstetrics and especially on the history of placenta previa, 160
- MENGERT, WILLIAM F., Venous ligation in obstetrics, 467 (Correspondence)
- , AND BOURLAND, J. W., The circulation of amniotic fluid, 79
- MILLEN, ROBERT S., Modified apparatus for tubal insufflation, 567
- MILLER, IRVIN, Suppurating fibromyomas: report of a case with a review of the literature, 522
- MILLER, LLOYD C. (WITH GAMBLE, THOMAS O., AND TANTER, M. L.), Benzyl penicillin—clinical toxicity and efficacy by mouth in impetigo in the newborn infant, 514
- MILLER, NORMAN F., WILLSON, J. ROBERT, AND COLLINS, JAMES, The surgical correction of congenital aplasia of the vagina, 735
- MITCHELL, ROBERT M., AND MOHLER, ROY W., Primary carcinoma of the Fallopian tube, 283
- MOHLER, ROY W. (WITH MITCHELL, ROBERT M.), Primary carcinoma of the Fallopian tube, 283
- , AND BISHOP, EDWARD H., Complete abdominal hysterectomy, 489
- MOORE, JOHN H., Leiomyoma of the ovary complicating pregnancy, 224
- MORRISON, J. HUFF, AND DOUGLASS, LOUIS H., Rupture of the uterus, 330

N

- NEVINS, THOMAS F. (WITH POLAYES, S. H.), Fetal hemorrhage from an angiomatous polyp of ileum complicating pregnancy, 207

- NEWTON, CHARLES W., JR., AND ANDROS, GEORGE J., Continuous caudal analgesia in curettage for abortion, 430
- NEWTON, LOUIS, Endometriosis of the abdominal scar, 561
- NICODEMUS, ROY E., RITMILLER, LEROY F., AND LEDDEN, LEWIS, J., Continuous caudal analgesia in obstetrics on trial, 312
- NORTON, JAMES F., AND ALTER, NICHOLAS M., Primary ovarian pregnancy, 535
- NOVAK, EMIL, AND STEVENSON, R. R., Sweat gland tumors of the vulva, benign (hidradenoma) and malignant (adenocarcinoma), 641

O

- O'TOOLE, LAWRENCE (WITH DOWNING, WENDELL), Parovarian cyst causing dystocia, 106

P

- PAGE, ERNEST W., AND BOYERS, L. MORGAN, Coccioid pelvic inflammatory disease, 212
- PATTON, GEORGE D., Diethylstilbestrol in the treatment of functional ovarian disorders, 417
- PHANEUF, L. E. (WITH SCHNALL, M. D., AND CONWAY, J. F.), Acute diverticulitis of the sigmoid in pregnancy, 558
- PHILLIPS, JOSEPH H., Studies concerning morbidity and mortality following hysterectomy, 174
- POLAYES, S. H., AND NEVINS, THOMAS F., Fatal hemorrhage from an angiomatous polyp of ileum complicating pregnancy, 207
- POSNER, A. CHARLES (WITH KUSHNER, J. IRVING), Craniotomy, with review of cases, 95
- POTTER, EDITH L., The effect on infant mortality of vitamin K administered during labor, 235

R

- RAKOFF, A. E. (WITH VAUX, NORRIS W.), estrogen-progesterone therapy; a new approach in the treatment of habitual abortion, 353
- RANDALL, JOHN H. (WITH ELLER, WILLIAM C.), Nausea of pregnancy treated by forced hydration, 518
- REID, ROGER D. (WITH BRADY, LEO), Lactobacillus therapy in vaginitis due to trichomonas, 509
- RIEMENSCHNEIDER, E. A. (WITH FAULKNER, ROBERT L.), Reactivation of endometriosis by stilbestrol therapy, 560
- RINEHART, ROBERT E., Serum protein in normal and toxemic pregnancy, 48
- RITMILLER, LEROY, F. (WITH NICODEMUS, ROY E., AND LEDDEN, LEWIS J.), Continuous caudal analgesia in obstetrics on trial, 312
- ROBY, CHARLES (WITH AABERG, MONRAD E.), Erythroblastosis fetalis in twin pregnancy, 548
- ROSENFELD, SAMUEL S., Paracervical anesthesia for the relief of labor pains, 527
- RUBENSTEIN, B. B., AND GUTERMAN, HENRY S., A simple technique for preparing vaginal smears, 565
- RUBIN, I. C., Therapeutic aspects of uterotubal insufflation in sterility, 621
- RUBY, BARBARA A. (WITH DIECKMANN, WILLIAM J., AND TURNER, DOROTHEA F.), Diet regulation and controlled weight in pregnancy, 701
- RUCKER, M. PIERCE (WITH HUDSON, GWEN S.), Gas bacillus infection of the uterus treated with penicillin, 452

S

- SAMPSON, JOHN A., The pathogenesis of postsalpingectomy endometriosis in laparotomy scars, 597

- SCHENK, K. W. (WITH CRAIG, IRWIN T.), Uterus didelphys complicating pregnancy, 556
- SCHMIDT, E. C. H., Complicated knot of the cord, 116 (Correspondence)
- SCHMITZ, EDGAR E., Double uterus, cervix, and vagina, with pregnancy carried to term, 555
- SCHMITZ, HERBERT E., AND BABA, GEORGE, Aquinone during labor; its effect on the prothrombin level of the newborn infant, 292
- SCHNALL, M. D., PHANEUF, L. E., AND CONWAY, J. F., Acute diverticulitis of the sigmoid in pregnancy, 558
- SCHNEIDER, EDWARD (WITH TRITSCH, JOHN E.), Clinical experience with a new synthetic ergonovine-like substance, 434
- SCHNEIDER, MAX, Pregnancy complicated by a subdural brain abscess, 550
- SCHUSTER, EUGENE B. (WITH FINEGOLD, WILFRED J.), Avulsion defects of the scalp of the newborn infant. Medicolegal implications, 108
- SEITCHIK, JOSEPH (WITH BURCH, LUCIUS E.), Ectopic gestation, 765
- SMITH, GEORGE VAN S., AND DRESSER, RICHARD, Carcinoma of the uterine cervix. Interval report on treatment, results, and complications, 1
- SNIDER, FRANKLIN F. (WITH KHA TI LIM), The effect of respiratory stimulants in the newborn infant, 146
- SPIVACK, MARY, Sick-cell anemia complicated by pregnancy, 442
- STEIN, IRVING F., A case of interstitial pregnancy with perforation and extensive intraperitoneal hemorrhage, 563
- , Bilateral polycystic ovaries. Significance in sterility, 385
- STEINBERG, MURRAY, Edema of the uvula and edema of the glottis—a reaction to demerol-scopolamine analgesia, 542
- STEINHORN, SEYMOUR R., The possible role of bacterial synergism in puerperal infections due to anaerobic streptococci, 63
- STEVENSON, R. R. (WITH NOVAK, EMIL), Sweat gland tumors of the vulva, benign (hidradenoma) and malignant (adenocarcinoma), 641
- STUDDIFORD, W. E., Further experiences in the use of transplanted abdominal fascia in the relief of stress incontinence, 119

T

- TAINTER, M. L. (WITH GAMBLE, THOMAS, AND MILLER, LLOYD C.), Benzyl penicillin—clinical toxicity and efficacy by mouth in impetigo in the newborn infant, 514
- TE LINDE, R. W. (WITH JONES, G. E. SEEGAR), The curability of granulosa-cell tumors, 691

- TRAUT, H. F., McIVOR, B. C., HOWARD, J., LUCIA, S. P., AND CHARVET, L., The Rh factor in obstetrics, 722
- TRITSCH, JOHN E. AND SCHNEIDER, EDWARD, Clinical experience with a new synthetic ergonovine-like substance, 434
- TURNER, DOROTHEA F. (WITH DIECKMANN, WILLIAM J., AND RUBY, BARBARA A.), Diet regulation and controlled weight in pregnancy, 701

V

- VAUX, NORRIS W., AND RAKOFF, A. E., Estrogen-progesterone therapy: a new approach in the treatment of habitual abortion, 353

W

- WATERMAN, GEORGE W., AND DiLEONE, RALPH, Treatment of carcinoma of the cervix by interstitial radium needles at the Rhode Island Hospital, 482
- WATERS, EDWARD G., The use of fine chromic catgut for postpartum perineal repair, 319
- WATSON, B. P., A quadriovular quadruplet pregnancy, 184
- WATTS, RUTH M., AND ADAIR, FRED L., A transplantable rat tumor, 11
- WEINBERG, C. H., Essential dysmenorrhea—its treatment with pavarine, 98
- WHELAN, CHARLES F. (WITH FALLON, JOHN, AND BROSNAN, JAMES T.), Differential stethoscope for determining patency of each tube, 568
- WILLIAM, GEORGE A., Phantom limb syndrome complicating pregnancy and puerperium, 546
- WILLIAMS, EDWIN L., Metastatic adenocarcinoma of the cervix uteri associated with primary gastric cancer, 342
- WILLIAMS, LAURA O. (WITH CHESLEY, LEON C.), Renal glomerular and tubular function in relation to the hyperuricemia of pre-eclampsia and eclampsia, 367
- WILLIAMSON, HERVEY C., AND GREELEY, ARTHUR V., Management of placenta previa, 398
- WILLSON, J. ROBERT, Carcinoma of the cervix complicated by pregnancy, 275
- (WITH MILLER, NORMAN F., AND COLLINS, JAMES), The surgical correction of congenital anlasia of the vagina, 735
- WILSON, KARL M., The role of Porro cesarean section in modern obstetrics, 761
- WOLTZ, JOHN H. E., AND ZINTEL, HAROLD A., The transmission of penicillin to amniotic fluid and fetal blood in the human, 338

Z

- ZINTEL, HAROLD A. (WITH WOLTZ, JOHN H. E.), The transmission of penicillin to amniotic fluid and fetal blood in the human, 338

SUBJECT INDEX*

A

- Abdominal fascia, transplanted, use of, in relief of stress incontinence, further experiences in (Studdiford), 119
- hysterectomy, complete (Mohler and Bishop), 489
- scar, endometriosis of (Newton), 581
- surgery, lower, use of cotton sutures in (Flax), 112 (Abst.)
- Abortion, 111, 459 (Absts.)
- criminal, air embolism in (Teare), 112 (Abst.)
- curettage for, continuous caudal analgesia in (Newton and Andros), 430
- habitual, estrogen-progesterone therapy (Vaux and Rakoff), 353
- therapy in (Ingram), 154
- spontaneous, threatened and habitual (Hertig and Livingstone), 459 (Abst.)
- sulfonamides in treatment of, preventive use of (Croisier), 111 (Abst.)
- Abscess, Bartholinian, use of carbolic acid in treatment of (Phelan), 113 (Abst.)
- brain, subdural, pregnancy complicated by (Schneider), 550
- Abstracts, abortion, 111, 459
- anatomy, anomalies, 111, 591
- anesthesia and analgesia, 591
- breasts, 591
- contraception, 352, 589
- fertility, 352, 589
- gynecologic operations, 112, 462
- labor, management, complications, 113, 463
- menstruation, dysmenorrhea, 230
- miscellaneous, 234
- newborn, 231, 465, 586
- pregnancy, complications, 347, 586
- physiology, diagnosis, 233
- puerperium, 349, 588
- radiation, 350
- Aburel's method induction of labor (Muñoz), 114 (Abst.)
- Adenocarcinoma of cervix uteri associated with primary gastric cancer (Williams), 342
- of endometrium, treatment in, results of various types of (McLennan), 254
- of vulva (Novak and Stevenson), 641
- Air embolism in criminal abortion (Teare), 112 (Abst.)
- Amenorrhea, oligomenorrhea, and anovulomenorrhea, studies in (Abarbanel and Leatham), 262
- war (Whitacre and Barerra), 230 (Abst.)
- American Board of Obstetrics and Gynecology, Inc., examinations, 466, 592 (Items)
- Journal of Obstetrics and Gynecology, 1920-1945, 595 (Editorial)
- Obstetrical and Gynecological Societies, roster of, 117, 469
- Amniotic fluid and fetal blood in the human, transmission of penicillin to (Woltz and Zintel), 338
- circulation of (Mengert and Bourland), 79
- Amyoplasia congenita causing malpresentation of fetus (Ealing), 115 (Abst.)
- Anaerobic streptococci, puerperal infections due to, possible role of bacterial synergism in (Steinhorn), 63
- Analgesia, caudal, continuous, in curettage for abortion (Newton and Andros), 430
- in obstetrics, experience with, at the University of Michigan Hospital (Andros and Henderson), 68
- on trial (Nicodemus et al.), 312

Analgesia, caudal—Cont'd

- in obstetrics, with special reference to repeated single blocks (Hanley and Malone), 306
- demerol-scopolamine, edema of uvula and edema of glottis a reaction to (Steinberg), 542
- spinal, in labor, continuous (Ramos et al.), 591 (Abst.)
- Anatomy, anomalies, 111, 591 (Absts.)
- Androgen therapy of menopausal symptoms in cancer patients (Gusberg), 502
- Anemia, sickle-cell, complicated by pregnancy (Spivack), 442
- Anesthesia, caudal, in private obstetric practice, five years' experience with (Baptisti), 180
- fractional spinal, cesarean section under (Levine), 75
- paracervical, for relief of labor pains (Rosenfeld), 527
- spinal, fractional, cesarean section under (Levine), 75
- Aneurysm of splenic artery with rupture complicating pregnancy (Danforth), 753
- Angiomatous polyp of ileum, fatal hemorrhage from, complicating pregnancy (Polayes and Nevins), 207
- Anovulomenorrhea, amenorrhea, and oligomenorrhea, studies in (Abarbanel and Leatham), 262
- Aplasia, congenital, of vagina, surgical correction of (Miller et al.), 735
- Aquinone during labor, its effect on prothrombin level of newborn infant (Schmitz and Baba), 292
- Arrhenoblastoma (Daughtry), 539
- Arthritis, gonorrheal, complicating pregnancy, treated with penicillin (Davis), 215
- Artificial impregnation, scope of, in barren marriage (Israel), 590 (Abst.)

B

- Bacterial synergism, possible role of, in puerperal infections due to anaerobic streptococci (Steinhorn), 63
- Bartholinian abscess, use of carbolic acid in treatment of (Phelan), 113 (Abst.)
- Benzyl penicillin, clinical toxicity and efficacy by mouth in impetigo in newborn infant (Gamble et al.), 514
- Blood, postpartum, on a nonclotting component of (Greenberg), 532
- pressure in normal pregnancy (Andros), 300
- Brain abscess, subdural, pregnancy complicated by (Schneider), 550
- Breasts, 591 (Absts.)

C

- Cancer of cervix, review of problem of, since use of radium in 1912 (Anspach), 681
- patients, androgen therapy of menopausal symptoms in (Gusberg), 502
- social service and (Abrams), 571 (Special article)
- uterine, diagnosis, value of cervical cytology smear in (Ayre et al.), 102
- Carbolic acid, use of, in treatment of Bartholinian abscess (Phelan), 113 (Abst.)
- Carcinoma, hypernephroid, of kidney or adrenal (?) and pregnancy (Lash), 221
- of breast, primary, sterilization of ovaries by roentgen rays in treatment of distant metastases from (Pohle), 350 (Abst.)

*July, pp. 1-118; August, pp. 119-234; September, pp. 235-352; October, pp. 353-470; November, pp. 471-594; December, pp. 595-770.

Carcinoma—Cont'd

- of cervix complicated by pregnancy (Willson), 275
 - treatment of, by interstitial radium needles at the Rhode Island Hospital (Waterman and DiLeone), 482
- of Fallopian tube, primary (Ayre et al.), 196; (Mitchell and Johler), 283
- of uterine cervix (Smith and Dresser), 1
- Catgut, fine chromic, use of, for postpartum perineal repair (Waters), 319
- Catharina Geertruida Schraders and her diary, note on history of obstetrics and especially on history of placenta previa (Marchetti), 160
- Catheter, passage of, through uterus into abdominal cavity (Elden), 569
- Caudal analgesia, continuous, in curettage for abortion (Newton and Andros), 430
 - in obstetrics, experience with, at the University of Michigan Hospital (Andros and Henderson), 68
 - on trial (Nicodemus et al.), 312
 - with special reference to repeated single blocks (Hanley and Malone), 306
 - in private obstetric practice, five years' experience with (Baptisti), 180
- Cervical cytology smear, value of, in uterine cancer diagnosis (Ayre et al.), 102
- stump, heminecrosis of, following supravaginal hysterectomy (Frank), 226
- Cervix, cancer of, review of problem of, since use of radium in 1912 (Ansach), 681
- cap, plastic, conception control by (Graffenberg and Dickinson), 352 (Abst.)
- carcinoma of, complicated by pregnancy (Willson), 275
 - treatment of, by interstitial radium needles at the Rhode Island Hospital (Waterman and DiLeone), 482
- uteri, ligaments attached to, exact anatomy and development of (Power), 111 (Abst.)
- metastatic adenocarcinoma of, associated with primary gastric cancer (Williams), 342
- uterine, carcinoma of (Smith and Dresser), 1
- Cesarean section, extraperitoneal, a peritoneal staining technique for (Bourgeois), 191
 - mortality (Dieckmann), 28
- Porro, role of, in modern obstetrics (Willson), 761
- ten years of, at the Boston Lying-In Hospital (Irving), 660
- under fractional spinal anesthesia (Levine), 75
- Chorionic gonadotropic hormone, reducing properties of, as related to the chemical determination of pregnancy (Bowman), 218
- Chromic catgut, use of fine, for postpartum perineal repair (Waters), 319
- Chylothorax in two-week-old infant, with spontaneous recovery (Wessel), 232 (Abst.)
- Circulation of amniotic fluid (Mengert and Bourland), 79
- Coccidioid pelvic inflammatory disease (Page and Boyers), 212
- Conception control by plastic cervix cap (Graffenberg and Dickinson), 352 (Abst.)
- Congenital aplasia of the vagina, surgical correction of (Miller et al.), 735
- Contraception, 352, 589 (Absts.)
- Cord, complicated knot of (Schmidt), 116 (Correspondence)
- Cornual resection for treatment of salpingitis (Falk), 462 (Abst.)
- Correspondence, complicated knot of the cord (Schmidt), 116
- venous ligation in obstetrics (Mengert), 468
- Cretinism in premature infant, epiphyseal dysgenesis associated with (Blatt et al.), 232 (Abst.)

- Culdoscopy (Decker and Cherry), 113 (Abst.)
- Curettage for abortion, continuous caudal analgesia in (Newton and Andros), 430
- Cyst, intraperitoneal nabothian (Frank), 107
- parovarian, causing dystocia (Downing and O'Toole), 106

D

- Demerol-scopolamine analgesia, edema of uvula and edema of glottis a reaction to (Steinberg), 542
- Depropanex, treatment of primary dysmenorrhea with (Grossmann), 411
- Dermoid cyst, mesenteric thrombosis complicated by (Lesh), 422
- Descensus uteri, vaginal hysterectomy in management of (Danforth), 376
- Diabetes in pregnancy (Kilkenny), 348 (Abst.)
- Diet regulation and controlled weight in pregnancy (Dieckmann et al.), 701
- Diethylstilbestrol in treatment of functional ovarian disorders (Patton), 417
- Diverticulitis, acute, of sigmoid in pregnancy (Schnall et al.), 558
- Dublin Lying-In (Rotunda) Hospital bicentenary (1745-1945) (Browne), 578 (Special article)
- Dysmenorrhea, 230 (Absts.)
 - essential, its treatment with pavatrine (Weinberg), 98
 - functional, treatment of, with pregnenolone (Harding), 56
 - primary, treatment of, with deproteinized pancreatic extract (Grossmann), 411
 - tubal insufflation in treatment of (Pineda), 590 (Abst.)
- Dystocia due to the shoulders (Barnum), 439
- parovarian cyst causing (Downing and O'Toole), 106
- prophylaxis of, through feto-maternal disproportion (Leon), 597 (Abst.)

E

- Eclampsia, renal glomerular and tubular function in relation to the hyperuricemia of pre-eclampsia and (Chesley and Williams), 367
 - seven-year review of, with special reference to treatment with veratrum viride (Green), 427
- Ectopic gestation (Burch and Seitchik), 765
- Edema of uvula and edema of glottis, a reaction to demerol-scopolamine analgesia (Steinberg), 542
- Endometriosis of abdominal scar (Newton), 561
 - postsalpingotomy, pathogenesis of, in laparotomy scars (Sampson), 597
 - reactivation of, by stilbestrol therapy (Faulkner and Riemenschneider), 560
- Endometrium, adenocarcinoma of, treatment in, results of various types of (McLennan), 254
- Epiphyseal dysgenesis associated with cretinism in premature infant (Blatt), 232 (Abst.)
- Equine and chorionic gonadotropins, treatment of hypoovarianism by sequential and cyclic administration of (Hamblen and Davis), 137
 - gonadotrophin, effect of, upon establishment of cyclic menses and ovulation (Abarbanel and Leatham), 262
- Ergonovine-like substance, synthetic, clinical experience with new (Tritsch and Schneider), 434
- Erythroblastosis fetalis (Macklin), 465 (Abst.)
 - comparison of newborn infants with, and those born to diabetic mothers (Miller et al.), 586
 - in twin pregnancy (Aaberg and Roby), 548
- Estrogen-progesterone therapy, new approach in treatment of habitual abortion (Vaux and Rakoff), 353

Extraperitoneal cesarean section, peritoneal staining technique for (Bourgeois), 191

F

Fallopian tube, carcinoma of, primary (Ayre et al.), 196; (Mitchell and Mohler), 283

Female sex hormones, search for (Frank), 757

Fertility, 352, 589 (Absts.)

Fetus, malpresentation of, amyoplasia congenita causing (Ealing), 115 (Abst.)

Fibromyoma, uterine, and pregnancy (Campos), 587 (Abst.)

Fibromyomas and pregnancy (de Rezende), 586 (Abst.)

suppurating, report of case, with review of literature (Miller), 522

G

Gas bacillus infection of uterus treated with penicillin (Hudson and Rucker), 452

Genital tuberculosis, pathogenesis and diagnosis of (Arana), 461 (Abst.)

Gestation, ectopic (Burch and Seitchik), 765

Gonadotrophic therapy, combined, comparative study of clinical responses of women with hypofunctioning ovaries to two methods of (Davis and Hamblen), 269

Gonadotropins, equine and chorionic, treatment of hypoovarianism by sequential and cyclic administration of (Hamblen and Davis), 137

Gonococcal vulvovaginitis, sulfonamide and stilbestrol therapy in (Hac et al.), 88

Gonorrheal arthritis complicating pregnancy, treated with penicillin (Davis), 215

Government and maternal welfare (Adair), 713

Granulosa-cell tumors, curability of (Jones and Te Linde), 691

Gynecologic operations, 112, 462 (Absts.)

Gynecology, 460 (Absts.)

H

Habitual abortion, therapy in (Ingram), 154

Hematomola of Breus, diagnostic difficulties increased by biologic reactions (Leon et al.), 347 (Abst.)

Heminecrosis of cervical stump following supravaginal hysterectomy (Frank), 226

Hemorrhage, fatal, from angiomatous polyp of ileum complicating pregnancy (Polayes and Nevins), 207

postpartum, injection of umbilical vein to prevent (McIntyre), 464 (Abst.)

Hernia, strangulated, containing pregnant uterus at term (Boys), 450

Hidradenoma of vulva (Novak and Stevenson), 641

Hogben pregnancy test, with note on breeding *Xenopus* for test (Landgrebe and Samson), 233 (Abst.)

Hormonal abnormalities, relationship between, and accidents of late pregnancy in diabetic women (Smith et al.), 349 (Abst.)

Hormone, chorionic gonadotropic, reducing properties of, as related to chemical determination of pregnancy (Bowman), 218

Hormones, female sex, search for (Frank), 757

Hypernephroid carcinoma of kidney or adrenal (?) and pregnancy (Lash), 221

Hyperplasia, normal and hyperactive ovary in (Hartman), 230 (Abst.)

Hypertrophy of uterus (Curtis), 748

Hyperuricemia of pre-eclampsia and eclampsia, renal glomerular and tubular function in relation to (Chesley and Williams), 367

Hypoovarianism, treatment of, by sequential and cyclic administration of equine and chorionic gonadotropins—so-called one-two cyclic gonadotropic therapy (Hamblen and Davis), 137

Hysterectomy, abdominal, complete (Mohler and Bishop), 489

morbidity and mortality following, studies concerning (Phillips), 174

partial, pregnancy at term after (Bunster), 347 (Abst.)

supravaginal, heminecrosis of cervical stump following (Frank), 226

vaginal (Emmert), 462 (Abst.)

in management of descensus uteri (Danforth), 376

I

Icterus neonatorum precox (Halbrecht), 232 (Abst.)

Impetigo in newborn infant, clinical toxicity and efficacy of benzyl penicillin by mouth in (Gamble et al.), 514

Incontinence, stress, use of transplanted abdominal fascia in relief of, further experiences in use of (Studdiford), 119

Infant deaths, study of, lessons to be learned from (Potter), 231 (Abst.)

mortality, effect on, of vitamin K administered during labor (Potter), 235

viability, should we change our present standard of? (Haas), 406

Interstitial pregnancy, case of, with perforation and extensive intraperitoneal hemorrhage (Stein), 563

Intraperitoneal nabothian cyst (Frank), 107

Intrauterine pastes (Weilerstein), 112 (Abst.)

Irradiation, effect of, on function of ovary in young girls (Kaplan), 340

Isometric method of x-ray pelvimetry as routine procedure (McLane), 495

Item, American Board of Obstetrics and Gynecology, Inc., examinations, 466, 592

Philadelphia Committee for Study of Pelvic Cancer, 592

Society of Obstetricians and Gynecologists of Canada, 115

K

Kidney, hypernephroid carcinoma of, and pregnancy (Lash), 221

Kymography and hystero-salpingography, indications for (Pineda), 590 (Abst.)

L

Labor, Aburel's method of induction of (Muñoz), 114 (Abst.)

aquinone during, its effect on prothrombin level of newborn infant (Schmitz and Baba), 292

induction of (Valenzuela), 113 (Abst.)

by Watson's method (Cabrera), 113 (Abst.)

management, complications, 113, 463 (Absts.)

pains, paracervical anesthesia for relief of (Rosenfeld), 527

placental senescence and onset of (Mandel et al.), 471

spinal analgesia in, continuous (Ramos), 591 (Abst.)

sudden death in (Cooke), 464 (Abst.)

test of (Danforth), 464 (Abst.)

third stage of, use of methergine in (Roberts), 464 (Abst.)

vitamin K administered during, effect on infant mortality (Potter), 235

Watson's method of induction of (Cabrera), 113 (Abst.)

Lactobacillus therapy in vaginitis due to trichomonas (Brady and Reid), 509

Laparotomy scars, postsalpingectomy endometriosis in, pathogenesis of (Samson), 597

Leiomyoma of ovary complicating pregnancy (Moore), 224

L-histidine monohydrochloride, nausea and vomiting of pregnancy treated with (Russo), 348 (Abst.)

M

- Malaria in connection with obstetrics and gynecology (Balasquide), 234 (Abst.)
- Maternal obstetrical paralysis (O'Connell), 115 (Abst.)
- weight gain, relationship of, and weight of newborn infant (Beilly and Kurland), 202
- welfare, government and (Adair), 713
- Menopausal symptoms, androgen therapy of, in cancer patients (Gusberg), 502
- Menopause, vitamin E in (Christy), 84
- Menses, cyclic, and ovulation, effect of equine gonadotrophin upon establishment of (Abarbanel and Leatham), 262
- Menstrual cycle in human cervical mucosa and its clinical significance (Wollner), 230 (Abst.)
- normal and hyperactive ovary in (Hartman), 230 (Abst.)
- Menstruation, 230 (Absts.)
- retarded, use of prostigmine to correct (Moll), 234 (Abst.)
- Mesenteric thrombosis complicated by dermoid cyst (Lesh), 422
- Metastatic adenocarcinoma of cervix uteri associated with primary gastric cancer (Williams), 342
- Methergine, a new oxytocic (Tollefson), 463 (Abst.)
- in third stage of labor (Roberts), 464 (Abst.)
- Mortality, cesarean section (Dieckmann), 28
- Myomectomy as conservative surgery (Borras), 463 (Abst.)
- Myxosarcoma of vagina associated with early pregnancy (Christie), 553

N

- Nabothian cyst, intraperitoneal (Frank), 107
- Nausea of pregnancy treated by forced hydration (Eller and Randall), 518
- Necrology, Seegar, J. K. B. E., 458
- Vineberg, Hiram Nahum, 110
- Vogt, William Hans, 229
- Watkins, Raymond Edward, 458
- Newborn, 231, 465, 586 (Absts.)
- infant, avulsion defects of scalp of (Finegold and Schuster), 108
- impetigo in, clinical toxicity and efficacy of benzyl penicillin by mouth in (Gamble), 514
- prothrombin level of, effect of aquinone during labor on (Schmitz and Baba), 292
- respiratory stimulants in, effect of (Lim and Snyder), 146
- teratoma of perineum in (Lash), 344
- weight of, relationship of maternal weight gain and (Beilly and Kurland), 202
- infants, oral moniliasis in (Anderson et al.), 232 (Abst.)
- jaundice of, role of hemoagglutinins anti-A and anti-B in pathogenesis of (Halbrecht), 232 (Abst.)
- Nipples, postpartum, fissured, prevention and treatment of, with local applications of vitamin A and D ointment (Brougher), 591 (Abst.)

O

- Obstetrics, analgesia in, continuous caudal, experience with, at the University of Michigan Hospital (Andros and Henderson), 68
- and gynecology, malaria in connection with (Balasquide), 234 (Abst.)
- caudal analgesia in, continuous, on trial (Nicodemus et al.), 312
- with special reference to repeated single blocks (Hanley and Malone), 306
- anesthesia in, five years' experience with (Baptisti), 180
- history of, Catharina Geertruida Schraders and her diary (Marchetti), 160
- Porro cesarean section in modern, role of (Wilson), 761
- Rh factor in (Halperin et al.), 326; (Traut et al.), 722
- venous ligation in (Mengert), 467 (Correspondence)

- Oligomenorrhea, amenorrhea, and anovulomenorrhea, studies in (Abarbanel and Leatham), 262
- One-two cyclic gonadotropic therapy (Hamblen and Davis), 137
- Ophthalmia neonatorum, penicillin in treatment of (Sievers), 465 (Abst.)
- Oral moniliasis in newborn infants (Anderson et al.), 232 (Abst.)
- Osteomalacia in pregnancy, case of (MacLennan), 348 (Abst.)
- Ovarian disorders, functional, diethylstilbestrol in treatment of (Patton), 417
- insufficiency, roentgen therapy in (Molinari), 350 (Abst.)
- pregnancy (Ballina and Chiodi), 456
- primary (Norton and Alter), 535
- tumors, spontaneous amputation of (Duran), 461 (Abst.)
- Ovaries, bilateral polycystic (Stein), 385
- hypofunctioning, comparative study of clinical responses of women with, to two methods of combined gonadotropic therapy (Davis and Hamblen), 269
- sterilization of, by roentgen rays in treatment of distant metastases from primary carcinoma of breast (Pohle), 350 (Abst.)
- Ovary, function of, in young girls, effect of irradiation on (Kaplan), 340
- leiomyoma of, complicating pregnancy (Moore), 224
- normal and hyperactive, in menstrual cycle and in hyperplasia (Hartman), 230 (Abst.)

P

- Pancreatic extract, deproteinized, treatment of primary dysmenorrhea with (Grossmann), 411
- Paracervical anesthesia for relief of labor pains (Rosenfeld), 527
- Paralysis, maternal obstetrical (O'Connell), 115 (Abst.)
- Parovarian cyst causing dystocia (Downing and O'Toole), 106
- Pavatrine, treatment of essential dysmenorrhea with (Weinberg), 98
- Pelvic inflammatory disease, coccidioidal (Page and Boyers), 212
- Pelvimetry, x-ray, isometric method of, as routine procedure (McLane), 495
- Pelviscopy in female, indications for (Harrell and Estevez), 462 (Abst.)
- Pelvis, clinically suspect, and its radiographical investigation in 1,000 cases (Kenny), 351 (Abst.)
- Penicillin, benzyl, clinical toxicity and efficacy by mouth in impetigo in newborn infant (Gamble et al.), 514
- gas bacillus infection of uterus treated with (Hudson and Rucker), 452
- gonorrheal arthritis complicating pregnancy treated with (Davis), 215
- in treatment of ophthalmia neonatorum (Sievers et al.), 465 (Abst.)
- puerperal sepsis treated with (White), 349 (Abst.)
- transmission of, to amniotic fluid and fetal blood in the human (Woltz and Zintel), 338
- Perineal repair, postpartum, use of fine chromic catgut for (Waters), 319
- Peritoneal staining technique for extraperitoneal cesarean section (Bourgeois), 191
- Peritonitis, postabortal (Garcia), 460 (Abst.)
- pathogenesis of (Falk and Blinick), 168
- Phenol, use of, in treatment of Bartholinian abscess (Phelan), 113 (Abst.)
- Philadelphia Committee for Study of Cancer, 592 (Item)
- Placenta previa, conservative management of some varieties of (Johnson), 248
- history of, Catharina Geertruida Schraders and her diary (Marchetti), 160
- management of, twelve-year study (Williamson and Greeley), 398
- Placental senescence and onset of labor (Mandel et al.), 471

Porro cesarean section in modern obstetrics, role of (Wilson), 761

Postabortal peritonitis (Garcia), 460 (Abst.)

pathogenesis of (Falk and Blinick), 168

Postpartum blood, on nonclotting component of (Greenberg), 532

hemorrhage, injection of umbilical vein to prevent (McIntyre), 464

perineal repair, use of fine chromic catgut for (Waters), 319

Postsalpingectomy endometriosis, pathogenesis of, in laparotomy scars (Sampson), 597

Pregnancy, acute diverticulitis of sigmoid in (Schnall et al.), 558

and puerperium, phantom limb syndrome complicating (Williams), 546

anemia, sickle-cell, complicated by (Spivack), 442

aneurysm of splenic artery with rupture complicating (Danforth), 753

angiomatous polyp of ileum complicating, fatal hemorrhage from (Polayes and Nevins), 207

at term after partial hysterectomy (Bunster), 347 (Abst.)

blood pressure in normal (Andros), 300

carcinoma of cervix complicated by (Willson), 275

chemical determination of, reducing properties of chorionic gonadotropic hormone as related to (Bowman), 218

complicated by subdural brain abscess (Schneider), 550

complications, 347, 586 (Absts.)

congenital absence of sacrum and coccyx complicating (Berman), 447

diabetes in (Kilkenny), 348 (Abst.)

double uterus, cervix, and vagina with, carried to term (Schmitz), 555

ectopic (Burch and Seitchik), 765

effect of, upon experimental hypertension in rabbit (Corbit), 233 (Abst.)

fatal hemorrhage from angiomatous polyp of ileum complicating (Polayes and Nevins), 207

fibromyomas and (de Rezende), 586 (Abst.)

gonorrheal arthritis complicating, treated with penicillin (Davis), 215

hypernephroid carcinoma of kidney or adrenal (?) and (Lash), 221

in diabetic women, relationship between hormonal abnormalities and accidents of late (Smith et al.), 349 (Abst.)

in diverticulum from uterus (Hawkins), 562

interstitial, case of, with perforation and extensive intraperitoneal hemorrhage (Stein), 563

leiomyoma of ovary complicating (Moore), 224

maternal rubella during, congenital dental defects in infants subsequent to (Evans), 591 (Abst.)

myxosarcoma of vagina associated with early (Christie), 553

nausea and vomiting of, treated with l-histidine monohydrochloride (Russo), 348 (Abst.)

treatment of, with vitamin B₁₂ (Varas), 347 (Abst.)

treated by forced hydration (Eller and Randall), 518

normal and toxemic, serum protein in (Rinehart), 48

osteomalacia in, case of (MacLennan), 348 (Abst.)

ovarian (Ballina and Chiodi), 456

primary (Norton and Alter), 535

physiology, diagnosis, 233 (Absts.)

quadriovular quadruplet (Watson), 184

serum protein in normal and toxemic (Rinehart), 48

sickle-cell anemia complicated by (Spivack), 442

test, Hogen, with note on breeding of Xenopus for test (Landgrebe and Samson), 233 (Abst.)

proliferative as (Moll), 234 (Abst.)

tumors and (Ramirez), 587 (Abst.)

twin, erythroblastosis fetalis in (Aaberg and Roby), 545

Pregnancy—Cont'd

uterine fibromyoma and (Campos), 587 (Abst.)

uterus didelphys complicating (Craig and Schenk), 556

vitamin C level in wartime, survey of (Craig et al.), 233 (Abst.)

weight in, controlled, diet regulation and (Dieckmann et al.), 701

Pregneninone, treatment of functional dysmenorrhea with (Harding), 56

Premature infant, epiphyseal dysgenesis associated with cretinism in (Blatt et al.), 232 (Abst.)

Premenstrual tension (Nogueira), 231 (Abst.)

Prostigmine, use of, as pregnancy test and to correct retarded menstruation (Moll), 234 (Abst.)

Prothrombin level of newborn infant, effect of aquinone during labor on (Schmitz and Baba), 292

Puerperal infections due to anaerobic streptococci, role of bacterial synergism in (Steinhorn), 63

sepsis, intrauterine sulfonamide therapy as prophylaxis in (Perez and Blanchard), 589 (Abst.)

surgery in (Aviles), 588 (Abst.)

treated with penicillin (White), 349 (Abst.)

Puerperium, 349, 588 (Absts.)

getting patients out of bed early in (Rotstein), 349 (Abst.)

Q

Quadriovular quadruplet pregnancy (Watson), 184

R

Radiation, 350 (Absts.)

Radium needles, interstitial, treatment of carcinoma of cervix by, at the Rhode Island Hospital (Waterman and DiLeone), 482

utero-vesical fistula after, case of (Willan and Shaw), 350 (Abst.)

Rat tumor, transplantable (Watts and Adair), 11

Renal glomerular and tubular function in relation to hyperuricemia of pre-eclampsia and eclampsia (Chesley and Williams), 367

Respiratory stimulants in newborn infant, effect of (Lim and Snyder), 146

Rh factor in obstetrics (Halperin et al.), 326; (Traut et al.), 722

Roentgen therapy in ovarian insufficiency (Molinari), 350 (Abst.)

Roster of American Obstetrical and Gynecological Societies, 117, 469

Round ligaments, new operation for shortening (Schneider), 462 (Abst.)

Rupture of uterus (Morrison and Douglass), 330

S

Sacrum and coccyx, congenital absence of, complicating pregnancy (Berman), 447

Salpingitis, cornual resection for treatment of (Falk), 462

Scalp of newborn infant, avulsion defects of (Finegold and Schuster), 108

Serum protein in normal and toxemic pregnancy (Rinehart), 48

Sickle-cell anemia complicated by pregnancy (Spivack), 442

Social service and cancer (Abrams), 571 (Special article)

Societies, roster of American Obstetrical and Gynecological, 117

Society of Obstetricians and Gynecologists of Canada, 115 (Item)

Spinal analgesia in labor, continuous (Ramos et al.), 591 (Abst.)

Spinelli operation for inversion of uterus, ruptured uterus following (Phaneuf), 463 (Abst.)

Splenic artery, aneurysm of, with rupture, complicating pregnancy (Danforth), 753

- Sterility, bilateral polycystic ovaries in (Stein), 385
 involuntary, treatment of, 589 (Abst.)
 problem (Pommerenke), 352 (Abst.)
 uterotubal insufflation in, therapeutic aspects of (Rubin), 621
- Stethoscope for determining patency of each tube, differential (Fallon et al.), 568
- Stilbestrol therapy, reactivation of endometriosis by (Faulkner and Riemen-schneider), 560
- Stillbirth in National Brazilian Institute of Puericulture (De Costa), 586 (Abst.)
- Strangulated hernia containing pregnant uterus at term (Boys), 450
- Sulfonamide and stilbestrol therapy in gonococcal vulvovaginitis (Hac et al.), 88
 compound, treatment of trichomonas vaginitis with (Angelucci), 336
- Sulfonamides in treatment of abortion, preventive use of (Croisier), 111 (Abst.)
- Surgery in puerperal sepsis (Aviles), 588 (Abst.)
 lower abdominal, use of cotton sutures in (Flax), 112 (Abst.)
- Surgical correction of congenital aplasia of vagina (Miller et al.), 735
- Sutures, cotton, use of, in lower abdominal surgery (Flax), 112 (Abst.)
- Sweat gland tumors of vulva, benign and malignant (Novak and Stevenson), 641
- Symphiotomy, partial (Costa), 114 (Abst.)
- Syndrome, phantom limb, complicating pregnancy and puerperium (Williams), 546
- Synthetic ergonovine-like substance, clinical experience with new (Tritsch and Schneider), 434

T

- Teratoma of perineum in newborn infant (Lash), 344
- Thiouracil storage in thyroid as affected by thyrotropic hormone and potassium iodide (Williams et al.), 460 (Abst.)
- Thyroid, thiouracil storage in, as affected by thyrotropic hormone and potassium iodide (Williams et al.), 460 (Abst.)
- Transplantable rat tumor (Watts and Adair), 11
- Transplanted abdominal fascia, use of, in relief of stress incontinence, further experiences in use of (Studdiford), 119
- Trichomonas vaginitis, treatment of, with sulfonamide compound (Angelucci), 336
- Tubal insufflation in treatment of dysmenorrhea (Pineda), 590 (Abst.)
 modified apparatus for (Millen), 567
 patency, simple technique to test (Decker), 227
- Tuberculosis, genital, pathogenesis and diagnosis (Arana), 461 (Abst.)
- Tumor, rat, transplantable (Watts and Adair), 11
- Tumors and pregnancy (Ramirez), 587 (Abst.)
 granulosa-cell, curability of (Jones and Te Linde), 691
 ovarian, spontaneous amputation of (Duran), 461 (Abst.)
 sweat gland, of vulva, benign and malignant (Novak and Stevenson), 641
- Twin pregnancy, erythroblastosis fetalis in (Aaberg and Roby), 548

U

- Ultraviolet irradiation of autotransfused blood in treatment of postabortal sepsis (Rebbeck), 459
- Uterine cancer diagnosis, cervical cytology smear in, value of (Ayre et al.), 102
 cervix, carcinoma of (Smith and Dresser), 1
 fibromyoma and pregnancy (Campos), 587 (Abst.)
 malformation (Olds et al.), 111 (Abst.)
- Uterotubal insufflation in sterility, therapeutic aspects of (Rubin), 621
- Utero-vesical fistula after radium, case of (Willan and Shaw), 350 (Abst.)
- Uterus, cervix, and vagina, double, with pregnancy carried to term (Schmitz), 555
 didelphys complicating pregnancy (Craig and Schenk), 556
 gas bacillus infection of, treated with penicillin (Hudson and Rucker), 452
 hypertrophy of (Curtis), 748
 pregnancy in diverticulum from (Hawkins), 562
 pregnant, at term, strangulated hernia containing (Boys), 450
 rupture of (Morrison and Douglass), 330
 Spinelli operation for, ruptured uterus following (Phaneuf), 463 (Abst.)

V

- Vagina, congenital aplasia of, surgical correction of (Miller et al.), 735
 myxosarcoma of, associated with early pregnancy (Christie), 553
- Vaginal hysterectomy (Emmert), 462 (Abst.)
 in management of descensus uteri, 376
 smears, simple technique for preparing (Rubenstein and Guterman), 565
- Vaginitis due to trichomonas, lactobacillus therapy in (Brady and Reid), 509
- Venous ligation in obstetrics (Mengert), 467 (Correspondence)
- Veratrum viride, treatment of eclampsia with, seven-year review (Greene), 427
- Vesicular mole, contribution to study of (Lima), 348 (Abst.)
- Vitamin B₆, treatment of nausea and vomiting of pregnancy with (Varas), 347 (Abst.)
 C level in wartime in pregnant women, survey of (Craig et al.), 233 (Abst.)
 E in menopause (Christy), 84
 K administered during labor, effect on infant mortality (Potter), 235
 therapy in menorrhagia (Gubner and Ungerleider), 231 (Abst.)
- Vulva, sweat gland tumors of, benign and malignant (Novak and Stevenson), 641
- Vulvovaginitis, gonococcal, sulfonamide and stilbestrol therapy in (Hac et al.), 88

W

- War amenorrhea (Whitacre and Barerra), 230 (Abst.)
- Watson's method of induction of labor (Cabrera), 113 (Abst.)
- Weight, controlled, in pregnancy, diet regulation and (Dieckmann et al.), 701
 gain, maternal, relationship of, and weight of newborn infant (Beilly and Kurland), 202

X

- X-ray pelvimetry, isometric method of, as routine procedure (McLane), 495

